

Complete if Known

Application Number	U.S. Patent 5,981,576
Filing Date	June 15, 1998
First Named Inventor	Michel Belley, et al
Examiner Name	
Group Art Unit	
Attorney Docket Number	

RECEIVED

SEP 20 2004

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT \$1,120

METHOD OF PAYMENT

☒ Deposit Account

Deposit Account Number

13-2755

Deposit Account Name

Merck & Co., Inc.

The Director is authorized to:

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) during the pendency of this application

FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Entity Fee (\$)	Fee Description	Fee Paid
1001	770	Utility filing fee	
1002	340	Design filing fee	
1004	770	Reissue filing fee	
1005	160	Provisional filing fee	

SUBTOTAL(1) \$0

2. EXTRA CLAIM FEES

	Extra	Fee from below	Fee Paid
Total Claims	20	0	0
Independent Claims	3	0	0
Multiple Dependent Claims		\$290	

\*\*or number previously paid, if greater; For Reissues, see below

Large Fee Code	Entity Fee (\$)	Fee Description
1202	18	Claims in excess of 20
1201	86	Independent claims in excess of 3
1203	290	Multiple dependent claim, if not paid
1204	86	**Reissue independent claims over original patent
1205	18	**Reissue claims in excess of 20 and over original patent

SUBTOTAL(2) \$0

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Entity Fee (\$)	Fee Description	Fee Paid
1051	130	Surcharge - late filing fee or oath	
1053	130	Non-English specification	
1812	2,520	For filing a request for <i>ex parte</i> reexamination	
1251	110	Extension for reply within first month	
1252	420	Extension for reply within second month	
1253	950	Extension for reply within third month	
1254	1,480	Extension for reply within fourth month	
1255	2,010	Extension for reply within fifth month	
1401	330	Notice of Appeal	
1402	330	Filing a brief in support of an appeal	
1403	290	Request for oral hearing	
1452	110	Petition to revive - unavoidable	
1453	1,330	Petition to revive - unintentional	
1501	1,330	Utility issue fee (or reissue)	
1502	480	Design issue fee	
1460	130	Petitions to the Commissioner	
1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	Submission of Information Disclosure Statement	
8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	Request for Continued Examination (RCE)	
Other fee (specify) Extension of Term of Patent			1,120
Other fee (specify) (37 C.F.R. 1.20(j)(i))			
SUBTOTAL(3)			\$1,120

SUBMITTED BY

Complete (if applicable)

Typed or Printed Name

Mitul I. Desai

Signature

Date

09/15/2004

Reg. Number

46,661

Deposit Account User ID



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

DAC  
\$

In Re: U.S. Patent 5,981,576  
Issued: November 9, 1999  
To: Michel Belley, et al.  
Assignee: Merck Frosst Canada & Co.  
For: (METHYLSULFONYL)PHENYL-2-(5H)-  
FURANONES AS COX-2 INHIBITORS

RECEIVED  
SEP 20 2004  
OFFICE OF PETITIONS

Mail Stop Patent Ext.  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156**

Sir:

Your applicant, Merck Frosst Canada & Co., a company organized and existing under the laws of Nova Scotia, Canada, represents that it is the owner of record of the entire interest in and to Letters Patent of the United States No. 5,981,576 granted to Michel Belley, et al. on November 9, 1999 for "(Methylsulfonyl)phenyl-2-(5H)-Furanones as Cox-2 Inhibitors" by virtue of an assignment from the inventors to Merck Frosst Canada, Inc. recorded July 23, 1999, Reel 010114, Frame 0350, and by virtue of a change of name from Merck Frosst Canada, Inc. to Merck Frosst Canada & Co. as a result of a reorganization recorded May 17, 2000, Reel 010822, Frame 0830.

Your Applicant acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). A copy of the Power of Attorney authorizing Mr. Mitul I. Desai to act on behalf of your Applicants is attached hereto as "Attachment A." For the convenience of the U.S. Patent

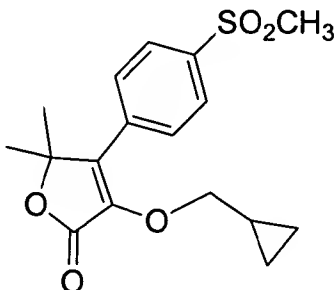
09/17/2004 CNGUYEN 00000045 132755 5981576

01 FC:1457 1120.00 DA

U.S. Patent No.: 5,981,576  
Patent Term Extension Appl'n  
Page No.: 2

and Trademark Office, the information contained in this application is presented in a format that follows the order of requirements of 37 C.F.R. § 1.740.

(a)(1) The approved product PREVICOX<sup>TM</sup> (firocoxib) is a cyclooxygenase-2 inhibitor and contains as the active ingredient firocoxib, having the chemical name 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one. The structural formula for firocoxib is as shown below:



(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 512 (21 U.S.C. § 360b).

(3) The approved product, PREVICOX<sup>TM</sup> (firocoxib) received permission for commercial marketing or use under Section 512 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 360b) on July 21, 2004.

(4) The only active ingredient in PREVICOX<sup>TM</sup> is firocoxib which has not been previously approved for commercial marketing or use under Section 512 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 360b) prior to the approval of NADA 141-230 by the Food and Drug Administration on July 21, 2004.

(5) This Application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f), said period which will expire on September 19, 2004.

(6) The complete identification of the patent for which extension is being sought is as follows:

Inventors: Michel Belley, Jacques Yves Gauthier, Erich Grimm, Yves LeBlanc, Chun-Sing Li, Michel Therien, Cameron Black, Petpiboon Prasit, Cheuk-Kun Lau, and Patrick Roy.

Patent Number: 5,981,576

Date of Issue: November 9, 1999

Current Date of Expiration: October 9, 2016.

(7) See "Attachment B" for a complete copy of the patent identified in paragraph (6) hereof.

(8) No disclaimer, certificate of correction or reexamination certificate has been issued with regard to US Patent No. 5,981,576. The Maintenance Fee Statement for U.S. Patent No. 5,981,576 is attached hereto as "Attachment C" and indicates that the fourth year maintenance fee was duly paid.

(9) U.S. Patent No. 5,981,576 claims the approved product and a method of using the approved product.

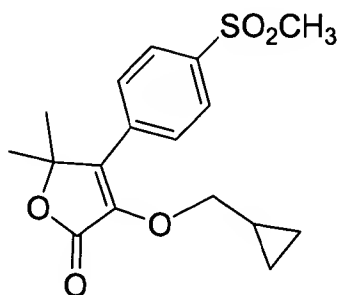
A listing of each applicable patent claim is: the active ingredient, firocoxib, is claimed as a compound in Claim 1; the active ingredient, firocoxib, is claimed as a pharmaceutical composition in Claim 2; and a method of using the active ingredient, firocoxib, is claimed in Claims 3, 4, 5, and 6.

(9)(i) The following analysis demonstrates the manner in which at least one such patent claim (e.g. Claim 1) reads on the approved product.

Claim 1 reads as follows:

1. A compound having the name  
3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one, or a  
pharmaceutically acceptable salt or hydrate thereof.

Claim 1 covers the compound 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one, which is firocoxib, represented by the structural formula shown below:



(9)(ii) The following analysis demonstrates the manner in which at least one such patent claim (e.g. Claims 4 and 5) reads on the method of using the approved product, where the claims include any claim to the method of using the approved product.

Claims 4 and 5 read as follows:

4. A method for treating a mammalian patient for a cyclooxygenase mediated disease comprising administering to a patient in need of such treatment a compound according to Claim 1 in an amount which is effective for treating said cyclooxygenase mediated disease.

5. A method in accordance with Claim 4 wherein the cyclooxygenase mediated disease is osteoarthritis, or rheumatoid arthritis.

The approved product PREVICOX<sup>TM</sup> (firocoxib) is a cyclooxygenase-2 inhibitor and has been approved for the control of pain and inflammation associated with osteoarthritis in dogs, and contains as an active ingredient firocoxib which is a compound of Claim 1 as described under the above analysis for Claim 1.



(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i)(A) Investigational New Animal Drug Application (INAD 010-348) for firocoxib was submitted on May 29, 1998 and the INAD became effective on June 29, 1998.

(B) New Animal Drug Application (NADA 141-230) PREVICOX™ (firocoxib) was submitted on April 15, 2004; and

(C) New Animal Drug Application (NADA 141-230) PREVICOX™ (firocoxib) was approved on July 21, 2004.

(11) As a brief description of the significant activities undertaken by the NADA Applicant, Merial Ltd., during the applicable regulatory review period, attached hereto as "Attachment D", is a chronology of the major communications between the NADA Applicant and the FDA from May 29, 1998 to July 21, 2004.

(12)(A) Applicant is of the opinion that U.S. Patent 5,981,576 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. § 156(a)

U.S. Patent 5,981,576 claims the approved product, a method of using the product and a method of manufacturing the product.

(b) 35 U.S.C. § 156(a)(1)

The term of U.S. Patent 5,981,576 has not expired before submission of this application under 35 U.S.C. § 156(d)(1) for its extension.

(c) 35 U.S.C. § 156(a)(2)

The term of U.S. Patent 5,981,576 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3)

The application for extension is submitted by the owner of record and is in accordance with the requirement of 35 U.S.C. § 156(d) and rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4)

The product, PREVICOX<sup>TM</sup> (firocoxib), has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A)

The permission for the commercial marketing or use of the product, PREVICOX<sup>TM</sup>, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4)

No other patent has been extended for the same regulatory review period for the product, PREVICOX<sup>TM</sup> (firocoxib).

(12)(B) The length of extension of the patent term of U.S. Patent 5,981,576 claimed by Applicant is 650 days or approx.1.78 years. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. 156(g)(1)(B) began on June 29, 1998 and ended on July 21, 2004 which is a total of 2214 days or 6.07 years which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. 156(g)(2)(B)(i), the "Testing Period," began on June 29, 1998 and ended on April 15, 2004, which is 2117 days or 5.80 years and

(ii) The period of review under 35 U.S.C. 156(g)(2)(B)(ii), the "Application Period," began on April 15, 2004 and ended on July 21, 2004, which is 97 days or 0.27 years;

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph (12)(B)(a) above ( 2214 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (June 29, 1998 to November 9, 1999) which is 498 days, and

(ii) The number of days during which applicant did not act with due diligence which is zero (0) days, and

(iii) One-half the number of days determined in sub-paragraph (12)(B)(a)(i) after the patent issued  $[(2117 - 498)/2]$  or 809 days;

(iv) The regulatory period is calculated by subtracting the number of days determined in sub-paragraph (12)(B)(b)(i)-(iii) from the entire regulatory review period as determined in sub-paragraph (12)(B)(a) (which is 2214 days – 498 days – 0 days – 809 days) which equals 907 days;

(c) The number of days as determined in sub-paragraph (12)(B)(b)(iv) (907) when added to the original term of the patent (October 9, 2016, as determined by 35 U.S.C. § 154 (c) and 37 C.F.R. § 1.321) would result in the date, April 4, 2019;

(d) Fourteen (14) years when added to the date of NADA approval (July 21, 2004) would result in the date July 21, 2018;

(e) The earlier date as determined in sub-paragraphs (12)(B)(c) and (12)(B)(d) is July 21, 2018;

(f) Since the original patent was not issued and a request for an exemption was not submitted before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, five (5) years when added to the original expiration date of the patent (October 9, 2016) would result in the date, October 9, 2021;

(g) The earlier date as determined in sub-paragraph (12)(B)(e) and (12)(B)(f) is July 21, 2018.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

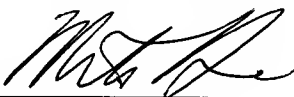
(14) The prescribed fee as set forth in 37 C.F.R. § 1.20(j)(1) for receiving and acting upon this application for extension is to be charged to Merck Deposit Account No. 13-2755 as authorized in the attached Fee Sheet, which is submitted in duplicate.

(15) Please address all inquiries and correspondence relating to the application for patent term extension to:

Mitul I. Desai  
Merck & Co., Inc.  
Patent Department  
P.O. Box 2000  
Rahway, New Jersey 07065-0907  
Telephone: (732) 594-3190  
Facsimile: (732) 594-1540

(16) The instant application for extension of patent term with regard to U.S. Patent No. 5,981,576 is being submitted as one original and triplicate copies thereof.

Respectfully submitted,

By 

Mitul I. Desai  
Reg. No. 46,661  
Attorney for Applicant

MERCK & CO., INC.  
P.O. Box 2000  
Rahway, New Jersey 07065-0907  
(732) 594-3190

Date: September 15, 2004


Attachments:

- "Attachment A" - Power of Attorney
- "Attachment B" - Copy of U.S. Patent Number: 5,981,576
- "Attachment C" - Maintenance Fee Statement for U.S. Patent No. 5,981,576
- "Attachment D"- Chronology of Major Communications with the FDA
- Fee Sheet

U.S. Patent No.: 5,981,576  
Patent Term Extension Appl'n  
Page No.: 14

**CERTIFICATION**

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and triplicate copies thereof.

By .  
\_\_\_\_\_  
Mitul I. Desai  
Reg. No. 46,661  
Attorney for Applicant

MERCK & CO., INC.  
P.O. Box 2000  
Rahway, New Jersey 07065-0907  
(732) 594-3190

Date: September 15, 2004

## **“Attachment A” – Power of Attorney**



**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

<b>In Re:</b>	U.S. Patent 5,981,576
<b>Issued:</b>	November 9, 1999
<b>To:</b>	Michel Belley, et al.
<b>Assignee:</b>	Merck Frosst Canada & Co.
<b>For:</b>	(METHYLSULFONYL)PHENYL-2-(5H)-FURANONES AS COX-2 INHIBITORS

Mail Stop Patent Ext.  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

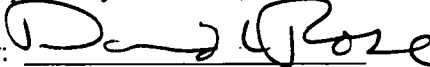
**POWER OF ATTORNEY**

Sir:

In connection with the above-identified patent, and in accordance with attached Merck General Corporate Resolution #5, the undersigned hereby appoints Mitul I. Desai Registration No. 46,661 and Raynard Yuro Registration No. 45,570 c/o MERCK & CO., INC., Patent Dept., RY60-30, P.O. Box 2000, Rahway, New Jersey 07065-0907, attorneys for the owner of record, to transact all business in the Patent and Trademark Office connected with the above-identified patent.

All communications in connection with the above-identified patent should be sent to Mitul I. Desai c/o MERCK & CO., INC., Patent Dept., RY60-30, P.O. Box 2000, Rahway, New Jersey 07065-0907.

Respectfully submitted,

By:   
David L. Rose  
Registration No. 26,332  
Attorney for Applicants

MERCK & CO., INC.  
P.O. Box 2000 - RY 60-30  
Rahway, New Jersey 07065-0907  
Telephone No. (732) 594-4777

Date: September 15, 2004  
Enclosures

**General Corporate Resolution #5**

**PATENT MATTERS**

RESOLVED, that any of the following:

Raymond V. Gilmartin-Chairman of the Board, President and Chief Executive Officer  
Kenneth C. Frazier-Senior Vice President and General Counsel  
Joseph F. DiPrima-Vice President and Assistant General Counsel  
Paul D. Matukaitis-Vice President and Assistant General Counsel  
Edward W. Murray-Counsel, Litigation  
Charles M. Caruso-Counsel, International  
Valerie J. Camara-Counsel, Patents  
Mark R. Daniel-Counsel, Patents  
Joanne M. Giesser-Counsel, Patents  
David L. Rose-Counsel, Patents  
Jack L. Tribble-Counsel, Patents  
Melvin Winokur-Counsel, Patents  
Donna L. Margiotto-Senior Manager, Patent Administration

are authorized to execute and to revoke on behalf of Merck & Co., Inc. and its affiliates (including subsidiaries) the following documents relating to patent matters:

Powers of attorney as fully in law as may be necessary and proper in connection with the acquisition, registration, maintenance and enforcement of patents and applications for patents, including powers of attorney relating to the prosecution or defense of patent rights before courts of law or other governmental tribunals, agencies or departments; affidavits and declarations; and any other documents which are necessary and proper for the acquisition, registration, maintenance, litigation and protection of patents.

CERTIFICATION

I, Debra A. Bollwage, Assistant Secretary of Merck & Co., Inc. (the "Corporation"), a corporation duly organized and existing under the laws of the State of New Jersey, do hereby certify that the attached, presently in full force and effect, is a true and correct copy of General Corporate Resolution #5, Patent Matters, as amended by Unanimous Written Consent of the Board of Directors of said Corporation on April 27, 2004.

IN WITNESS WHEREOF, I have hereunto subscribed my signature and affixed the seal of the Corporation this 28<sup>th</sup> day of April 2004.

Debra A. Bollwage  
Assistant Secretary

(SEAL)

**“Attachment B”**  
**Copy of US Patent No. 5,981,576**



US005981576A

**United States Patent** [19]

Belley et al.

[11] **Patent Number:** **5,981,576**[45] **Date of Patent:** **Nov. 9, 1999**[54] **(METHYLSULFONYL)PHENYL-2-(5H)-  
FURANONES AS COX-2 INHIBITORS**

[75] **Inventors:** Michel Belley, Pierrefonds; Jacques Yves Gauthier, Laval; Erich Grimm, Baie D'Urfe; Yves LeBlanc, Kirkland; Chun-Sing Li, Dollard Des Ormeaux; Michel Therien, Laval; Cameron Black, Pointe Claire; Petplboon Prasit, Kirkland; Cheuk-Kun Lau, Ile Bizard; Patrick Roy, Dollard Des Ormeaux, all of Canada

[73] **Assignee:** Merck Frosst Canada, Inc., Kirkland, Canada

[21] **Appl. No.:** 09/097,537

[22] **Filed:** Jun. 15, 1998

**Related U.S. Application Data**

[63] Continuation-in-part of application No. 08/728,512, Oct. 9, 1996, abandoned

[60] Provisional application No. 60/005,371, Oct. 13, 1995, and provisional application No. 60/011,637, Feb. 14, 1996.

[51] **Int. Cl.<sup>6</sup>** ..... C07D 307/02; A61K 31/34

[52] **U.S. Cl.** ..... 514/473; 549/477

[58] **Field of Search** ..... 549/477; 514/473

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

5,474,995 12/1995 Ducharme et al. .... 514/241  
5,480,568 1/1996 Pawloski et al. .... 252/46.7

**FOREIGN PATENT DOCUMENTS**

WO 91/16055 10/1991 WIPO .

WO 95/00501 1/1995 WIPO .

WO 95/05376 2/1995 WIPO .

WO 96/19469 6/1996 WIPO .

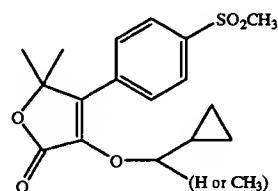
**OTHER PUBLICATIONS**

James J. Li, et al., J. of Med Chem., vol. 38, No. 22, pp. 4570-4578 (1995).

*Primary Examiner*—Zinna Northington Davis  
*Attorney, Agent, or Firm*—Richard C. Billups; David L. Rose

[57] **ABSTRACT**

The invention encompasses the novel compound of Formula A that is useful in the treatment of cyclooxygenase-2 mediated diseases.



The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula A.

**12 Claims, No Drawings**

(METHYLSULFONYL)PHENYL-2-(5H)-  
FURANONES AS COX-2 INHIBITORS

CROSS-REFERENCE TO RELATED  
APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 08/728,512 filed on Oct. 9, 1996, abandoned, which was based upon provisional application Ser. Nos. 60/005,371 filed on Oct. 13, 1995 and 60/011,637 filed on Feb. 14, 1996, priority of which is claimed hereunder.

BACKGROUND OF THE INVENTION

This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

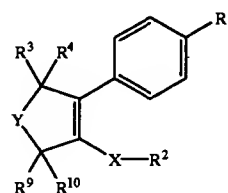
Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase, cyclooxygenase-2 (COX-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the COX-1 which has been cloned, sequenced and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, COX-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, COX-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, COX-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of COX-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

Furthermore, such a compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis) and for the treatment of glaucoma.

A brief description of the potential utility of cyclooxygenase-2 inhibitors is given in an article by John Vane, *Nature*, Vol. 367, pp. 215-216, 1994, and in an article in *Drug News and Perspectives*, Vol. 7, pp. 501-512, 1994.

SUMMARY OF THE INVENTION

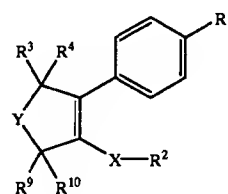
The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula I.

DETAILED DESCRIPTION OF THE  
INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



or a pharmaceutically acceptable salt thereof wherein:

X is selected from the group consisting of

- (a) CH<sub>2</sub>,
- (b) CHOH,
- (c) CO,
- (d) O,
- (e) S, and
- (f) N(R<sup>15</sup>),

with the proviso that when R<sup>3</sup> and R<sup>4</sup> are other than

- (1) both hydrogen,
- (2) both C<sub>1-10</sub> alkyl, or
- (3) joined together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, then

X is selected from CO, O, S or N(R<sup>15</sup>);

Y is selected from the group consisting of

- (a) C(R<sup>11</sup>)(R<sup>12</sup>),
- (b) CO,
- (c) O, and
- (d) S;

R<sup>1</sup> is selected from the group consisting of

- (a) SO<sub>2</sub>CH<sub>3</sub>,
- (b) SO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>,
- (c) SO<sub>2</sub>NHC(O)CF<sub>3</sub>,

- (d)  $S(O)(NH)NH_2$ ,  
 (e)  $S(O)(NH)NHC(O)CF_3$ ,  
 (f)  $P(O)(CH_3)NH_2$ , and  
 (g)  $P(O)(CH_3)_2$ ,  
 $R^2$  is selected from the group consisting of
- (a)  $C_{1-10}$ alkyl,
  - (b) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of
    - (1) hydrogen,
    - (2) halo,
    - (3)  $C_{1-10}$ alkoxy,
    - (4)  $C_{1-10}$ alkylthio,
    - (5) CN,
    - (6)  $C_{1-6}$ fluoroalkyl
    - (7)  $C_{1-10}$ alkyl,
    - (8)  $N_3$ ,
    - (9)  $-CO_2H$ ,
    - (10)  $-CO_2-C_{1-10}$ alkyl,
    - (11)  $-C(R^5)(R^6)-OH$ ,
    - (12)  $-C(R^5)(R^6)-O-C_{1-4}$ alkyl, and
    - (13)  $-C_{1-6}$ alkyl- $CO_2-R^5$ ,
    - (14) benzyloxy,
    - (15)  $-O-(C_{1-6}$ alkyl)- $CO_2R^5$ , and
    - (16)  $-O-(C_{1-6}$ alkyl)- $NR^5R^6$ ,
  - (c) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic aromatic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein the substituents are selected from the group consisting of
    - (1) hydrogen,
    - (2) halo,
    - (3)  $C_{1-10}$ alkyl,
    - (4)  $C_{1-10}$ alkoxy,
    - (5)  $C_{1-10}$ alkylthio,
    - (6) CN,
    - (7)  $CF_3$ ,
    - (8)  $N_3$ ,
    - (9)  $-C(R^5)(R^6)-OH$ ,
    - (10)  $-C(R^5)(R^6)-O-C_{1-10}$ alkyl, and
    - (11)  $C_{1-6}$ fluoroalkyl;
  - (d) a mono- or di-substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; wherein the substituents are selected from the group consisting of
    - (1) hydrogen,
    - (2) halo,
    - (3)  $Cl$ -loalkyl,
    - (4)  $C_{1-10}$ alkoxy,
    - (5)  $C_{1-10}$ alkylthio,
    - (6) CN,
    - (7)  $CF_3$ ,
    - (8)  $N_3$ ,
    - (9)  $-C(R^5)(R^6)-OH$ ,
    - (10)  $-C(R^5)(R^6)-O-C_{1-10}$ alkyl, and
    - (11)  $C_{1-6}$ fluoroalkyl;
  - (e) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.
  - (f) a mono- or di-substituted benzocarbocycle in which the carbocycle is a 5, 6, or 7-membered ring which

optionally contains a carbonyl group, wherein the substituents are selected from the group consisting of

- (1) hydrogen,
  - (2) halo,
  - (3)  $C_{1-10}$ alkyl,
  - (4)  $C_{1-10}$ alkoxy,
  - (5)  $C_{1-10}$ alkylthio,
  - (6) CN,
  - (7)  $CF_3$ ,
  - (8)  $N_3$ ,
  - (9)  $-C(R^5)(R^6)-OH$ ,
  - (10)  $-C(R^5)(R^6)-O-C_{1-10}$ alkyl, and
  - (11)  $C_{1-6}$ fluoroalkyl;
- (g) a mono- or di-substituted bicyclic heteroaryl of 8, 9, or 10 members, containing 2 to 5 heteroatoms chosen independently from O, S or N, and in which each ring contains at least one heteroatom, wherein the substituents are selected from the group consisting of
- (1) hydrogen,
  - (2) halo,
  - (3)  $C_{1-10}$ alkyl,
  - (4)  $C_{1-10}$ alkoxy,
  - (5)  $C_{1-10}$ alkylthio,
  - (6) CN,
  - (7)  $CF_3$ ,
  - (8)  $N_3$ ,
  - (9)  $-C(R^5)(R^6)-OH$ ,
  - (10)  $-C(R^5)(R^6)-O-C_{1-10}$ alkyl, and
  - (11)  $C_{1-6}$ fluoroalkyl;
- $R^3$  is hydrogen,  $C_{1-10}$  alkyl,  $CH_2OR^7$ , CN,  $CH_2CN$ ,  $C_{1-6}$ fluoroalkyl, F,  $CON(R^7)_2$ , mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of
- (1) hydrogen,
  - (2) halo,
  - (3)  $C_{1-6}$ alkyl,
  - (4)  $C_{1-6}$ alkoxy,
  - (5)  $C_{1-6}$ alkylthio,
  - (6) CN,
  - (7)  $CF_3$ ,
  - (8)  $N_3$ ,
  - (9)  $-C(R^5)(R^6)-OH$ ,
  - (10)  $-C(R^5)(R^6)-O-C_{1-4}$ alkyl, and
  - (11)  $C_{1-6}$ fluoroalkyl;
- $R^4$  is
- (a) hydrogen
  - (b)  $C_{1-10}$ alkyl,
  - (c)  $C_{1-10}$ alkoxy,
  - (d)  $C_{1-10}$ alkylthio,
  - (e)  $-OH$ ,
  - (f)  $-OCOR^7$ ,
  - (g)  $-SH$ ,
  - (h)  $-SCOR^7$ ,
  - (i)  $-OCO_2R^8$ ,
  - (j)  $-SCO_2R^8$ ,
  - (k)  $OCON(R^7)_2$ ,
  - (l)  $SCON(R^7)_2$ , and
  - (m)  $C_{1-6}$ fluoroalkyl;
- or  $R^3$  and  $R^4$  together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

## 5

R<sup>5</sup> and R<sup>6</sup> are each independently selected from the group consisting of

(a) hydrogen, and

(b) C<sub>1-10</sub>alkyl,

or R<sup>5</sup> and R<sup>6</sup> together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

each R<sup>7</sup> is independently selected from the group consisting of

(a) hydrogen,

(b) C<sub>1-6</sub>alkyl,

(c) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, CN, or CF<sub>3</sub>, and

(d) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, CN, or CF<sub>3</sub>, or

two R<sub>7</sub> groups taken together with the nitrogen to which they are attached form a saturated monocyclic ring of 5, 6 or 7 atoms, optionally containing an additional O, S or NR<sup>5</sup>;

each R<sup>8</sup> is independently selected from the group consisting of

(a) C<sub>1-6</sub>alkyl,

(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, CN, or CF<sub>3</sub>, and

(c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, CN, or CF<sub>3</sub>;

R<sup>9</sup> and R<sup>10</sup> are independently selected from the group consisting of:

(a) hydrogen, and

(b) C<sub>1-7</sub>alkyl, or

R<sup>9</sup> and R<sup>10</sup> together with the carbon atom to which they are attached form a carbonyl or thiocarbonyl group;

R<sup>11</sup> and R<sup>12</sup> are independently

(a) hydrogen,

(b) mono- or di-substituted phenyl or mono- or di-substituted benzyl or mono- or di-substituted heteroaryl or mono- or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) fluoro, chloro, bromo and iodo,

(3) C<sub>1-6</sub>alkyl,

(4) C<sub>1-6</sub>alkoxy,

(5) C<sub>1-6</sub>alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) N<sub>3</sub>,

(9) —C(R<sup>13</sup>)(R<sup>14</sup>)—OH,

(10) —C(R<sup>13</sup>)(R<sup>14</sup>)—O—C<sub>1-4</sub>alkyl, and

(11) C<sub>1-6</sub>fluoroalkyl, or

(c) C<sub>1-7</sub>alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1-6</sub>fluoroalkyl, CON(R<sup>7</sup>)<sub>2</sub>, F, or OR<sup>7</sup>; or

R<sup>11</sup> and R<sup>12</sup> together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R<sup>13</sup> and R<sup>14</sup> are independently selected from the group consisting of:

(a) hydrogen,

(b) C<sub>1-7</sub>alkyl, or

## 6

R<sup>13</sup> and R<sup>14</sup> together with the carbon to which they are attached form a carbonyl, —C(=S)—, or a saturated monocyclic carbon ring of 3, 4, 5, 6, or 7 atoms.

R<sup>15</sup> is selected from the group consisting of:

(a) hydrogen,

(b) C<sub>1-10</sub>alkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-10</sub>alkoxy,

(4) C<sub>1-10</sub>alkylthio,

(5) CN,

(6) C<sub>1-6</sub>fluoroalkyl

(7) C<sub>1-10</sub>alkyl,

(8) N<sub>3</sub>,

(9) —CO<sub>2</sub>H,

(10) —CO<sub>2</sub>—C<sub>1-10</sub>alkyl,

(11) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH,

(12) —C(R<sup>5</sup>)(R<sup>6</sup>)—O—C<sub>1-4</sub>alkyl, and

(13) —C<sub>1-6</sub>alkyl—CO<sub>2</sub>—R<sup>5</sup>;

(14) benzyloxy,

(15) —O—(C<sub>1-6</sub>alkyl)—CO<sub>2</sub>R<sup>5</sup>, and

(16) —O—(C<sub>1-6</sub>alkyl)—NR<sup>5</sup>R<sup>6</sup>,

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-10</sub>alkyl,

(4) C<sub>1-10</sub>alkoxy,

(5) C<sub>1-10</sub>alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) N<sub>3</sub>,

(9) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH,

(10) —C(R<sup>5</sup>)(R<sup>6</sup>)—O—C<sub>1-10</sub>alkyl, and

(11) C<sub>1-6</sub>fluoroalkyl;

(e) a mono- or di-substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-10</sub>alkyl,

(4) C<sub>1-10</sub>alkoxy,

(5) C<sub>1-10</sub>alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) N<sub>3</sub>,

(9) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH,

(10) —C(R<sup>5</sup>)(R<sup>6</sup>)—O—C<sub>1-10</sub>alkyl, and

(11) C<sub>1-6</sub>fluoroalkyl;

(f) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.

(g) a mono- or di-substituted benzocarbocycle in which the carbocycle is a 5, 6, or 7-membered ring which



optionally contains a carbonyl group, wherein the substituents are selected from the group consisting of

- (1) hydrogen,
- (2) halo,
- (3) C<sub>1-10</sub>alkyl,
- (4) C<sub>1-10</sub>alkoxy,
- (5) C<sub>1-10</sub>alkylthio,
- (6) CN,
- (7) CF<sub>3</sub>,
- (8) N<sub>3</sub>,
- (9) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH,
- (10) —C(R<sup>5</sup>)(R<sup>6</sup>)—O—C<sub>1-4</sub>alkyl, and
- (11) C<sub>1-6</sub>fluoroalkyl;

R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of

- (a) hydrogen
- (b) C<sub>1-10</sub>alkyl,
- (c) C<sub>1-10</sub>alkanoic acid,
- (d) C<sub>1-10</sub>alkyl amine,
- (e) phenyl or monosubstituted phenyl wherein the substituents are halo, C<sub>1-10</sub>alkyl, C<sub>1-10</sub>alkoxy, C<sub>1-10</sub>alkylthio, C<sub>1-10</sub>alkanoic acid, C<sub>1-10</sub>alkylamine, CN, CO<sub>2</sub>H or CF<sub>3</sub>, and
- (f) benzyl or monosubstituted benzyl wherein the substituents are halo, C<sub>1-10</sub>alkyl, C<sub>1-10</sub>alkoxy, C<sub>1-10</sub>alkylthio, C<sub>1-10</sub>alkanoic acid, C<sub>1-10</sub>alkylamine, CN, COOH or CF<sub>3</sub>, or

R<sup>16</sup> and R<sup>17</sup> together with the nitrogen to which they are attached form a saturated monocyclic ring of 5, 6 or 7 atoms, optionally containing an additional O, S or NR<sup>5</sup>.

Within this embodiment there is a genus of compounds wherein

R<sup>9</sup> and R<sup>10</sup> together with carbon atom to which they are attached form a carbonyl.

Within this genus there is a class of compounds wherein

X is O;

Y is O;

R<sup>1</sup> is selected from the group consisting of

- (a) SO<sub>2</sub>CH<sub>3</sub>,
- (b) S(O)<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>, and
- (c) S(O)(NH)NH<sub>2</sub>;

R<sup>2</sup> is selected from the group consisting of

mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of

- (1) hydrogen,
- (2) halo,
- (3) C<sub>1-4</sub>alkoxy,
- (4) C<sub>1-4</sub>alkylthio,
- (5) CN,
- (6) C<sub>1-3</sub> fluoroalkyl
- (7) C<sub>1-4</sub> alkyl,
- (8) —CO<sub>2</sub>H,
- (9) —CO<sub>2</sub>—C<sub>1-10</sub>alkyl,
- (10) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH,

R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1-4</sub>fluoroalkyl, F, CON(R<sup>7</sup>)<sub>2</sub>, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

- (1) hydrogen,
- (2) halo,

- (3) C<sub>1-4</sub>alkyl,
- (4) C<sub>1-4</sub>alkoxy,
- (5) C<sub>1-4</sub>alkylthio,
- (6) CN,
- (7) CF<sub>3</sub>,
- (8) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH, and

R<sup>4</sup> is

- (a) hydrogen
- (b) C<sub>1-6</sub>alkyl,
- (c) C<sub>1-6</sub>alkoxy,
- (d) C<sub>1-6</sub>alkylthio,
- (e) —OH,
- (f) —OCOR<sup>7</sup>,
- (g) —SCOR<sup>7</sup>,
- (h) —OCO<sub>2</sub>R<sup>8</sup>, and
- (i) —SCO<sub>2</sub>R<sup>8</sup>,

or R<sup>3</sup> and R<sup>4</sup> together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R<sup>5</sup> and R<sup>6</sup> are each independently selected from the group consisting of

- (a) hydrogen, and
- (b) C<sub>1-6</sub>alkyl,

or R<sup>5</sup> and R<sup>6</sup> together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

each R<sup>7</sup> is independently selected from the group consisting of

- (a) hydrogen,
- (b) C<sub>1-4</sub>alkyl,
- (c) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>, and
- (d) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>

each R<sup>8</sup> is independently selected from the group consisting of

- (a) C<sub>1-4</sub>alkyl,
- (b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>, and
- (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>;

R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are connected form a carbonyl;

R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of

- (a) hydrogen
- (b) C<sub>1-6</sub>alkyl,
- (c) C<sub>1-6</sub>alkanoic acid,
- (d) C<sub>1-6</sub>alkyl amine,
- (e) phenyl or monosubstituted phenyl wherein the substituents are halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, C<sub>1-6</sub>alkanoic acid, C<sub>1-6</sub>alkylamine, CN, CO<sub>2</sub>H or CF<sub>3</sub>, and
- (f) benzyl or monosubstituted benzyl wherein the substituents are halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, C<sub>1-6</sub>alkanoic acid, C<sub>1-6</sub>alkylamine, CN, CO<sub>2</sub>H or CF<sub>3</sub>.

Within this class there is a sub-class of compounds wherein

X is O;

Y is O;

R<sup>1</sup> is selected from the group consisting of

(a) SO<sub>2</sub>CH<sub>3</sub>, and

(b) SO<sub>2</sub>NR<sup>16</sup>R<sup>7</sup>;

R<sup>2</sup> is selected from the group consisting of

mono- or di-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(5) CN,

(6) CF<sub>3</sub>, and

(7) C<sub>1-4</sub> alkyl,

R<sup>3</sup> is hydrogen or C<sub>1-3</sub> alkyl;

R<sup>4</sup> is hydrogen or C<sub>1-3</sub> alkyl;

R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are connected form a carbonyl. R<sup>16</sup> and R<sup>17</sup> equal to hydrogen is preferred.

Within this sub-class there is a group of compounds wherein

X is O;

Y is O;

R<sup>1</sup> is selected from the group consisting of

(a) SO<sub>2</sub>CH<sub>3</sub>, and

(b) SO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>;

R<sup>2</sup> is selected from the group consisting of

mono- or di-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(5) CN,

(6) CF<sub>3</sub>, and

(7) C<sub>1-4</sub> alkyl,

R<sup>3</sup> is methyl or ethyl;

R<sup>4</sup> is methyl or ethyl; and

R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are connected form a carbonyl.

Within the above embodiment there is another genus of compounds wherein

X is selected from the group consisting of

(a) CH<sub>2</sub>, and

(b) O,

Y is selected from the group consisting of

(a) CH<sub>2</sub>, and

(b) O,

R<sup>1</sup> is selected from the group consisting of

(a) SO<sub>2</sub>CH<sub>3</sub>,

(b) SO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>, and

(c) S(O)(NH)NH<sub>2</sub>;

R<sup>2</sup> is selected from the group consisting of

(a) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-6</sub> alkyl,

(4) C<sub>1-6</sub> alkoxy,

(5) C<sub>1-6</sub> alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH, and

(b) a mono- or di-substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-6</sub> alkyl,

(4) C<sub>1-6</sub> alkoxy,

(5) C<sub>1-10</sub> alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH, and

(c) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.

(d) a mono- or di-substituted benzocarbocycle in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-6</sub> alkyl,

(4) C<sub>1-6</sub> alkoxy,

(5) C<sub>1-6</sub> alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH, and

(e) a mono- or di-substituted bicyclic heteroaryl of 8, 9, or 10 members, containing 2, 3, 4 or 5 heteroatoms chosen independently from O, S or N, and in which each ring contains at least one heteroatom, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-6</sub> alkyl,

(4) C<sub>1-6</sub> alkoxy,

(5) C<sub>1-6</sub> alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH, and

R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1-3</sub> fluoroalkyl, F, CON(R<sup>7</sup>)<sub>2</sub>, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-4</sub> alkyl,

(4) C<sub>1-4</sub> alkoxy,

(5) C<sub>1-4</sub> alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH, and

R<sup>4</sup> is

(a) hydrogen

(b) C<sub>1-4</sub> alkyl,

(c) C<sub>1-4</sub> alkoxy,

- (d) C<sub>1-4</sub>alkylthio,  
 (e) —OH,  
 (f) —OCOR<sup>7</sup>,  
 (g) —SCOR<sup>7</sup>,  
 (h) —OCO<sub>2</sub>R<sup>8</sup>, and  
 (i) —SCO<sub>2</sub>R<sup>8</sup>,  
 or R<sup>3</sup> and R<sup>4</sup> together with the carbon to which they are  
 attached form a saturated monocyclic carbon ring of 3, 4,  
 5, 6 or 7 atoms; R<sup>5</sup> and R<sup>6</sup> are each independently selected  
 from the group consisting of  
 (a) hydrogen, and  
 (b) C<sub>1-4</sub>alkyl,  
 or R<sup>5</sup> and R<sup>6</sup> together with the atom to which they are  
 attached form a saturated monocyclic ring of 3, 4, 5, 6  
 or 7 atoms;  
 each R<sup>7</sup> is independently selected from the group consisting  
 of  
 (a) hydrogen,  
 (b) C<sub>1-4</sub>alkyl,  
 (c) phenyl or monosubstituted phenyl wherein the sub-  
 stituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy,  
 C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>, and  
 (d) benzyl or monosubstituted benzyl wherein the sub-  
 stituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy,  
 C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>,  
 each R<sup>8</sup> is independently selected from the group consisting  
 of  
 (a) C<sub>1-4</sub>alkyl,  
 (b) phenyl or monosubstituted phenyl wherein the sub-  
 stituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy,  
 C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>, and  
 (c) benzyl or monosubstituted benzyl wherein the sub-  
 stituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy,  
 C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>;  
 R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are  
 connected form a carbonyl;  
 R<sup>16</sup> and R<sup>17</sup> are independently selected from the group  
 consisting of  
 (a) hydrogen  
 (b) C<sub>1-6</sub>alkyl,  
 (c) C<sub>1-6</sub>alkanoic acid,  
 (d) C<sub>1-6</sub>alkyl amine,  
 (e) phenyl or monosubstituted phenyl wherein the sub-  
 stituents are halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio,  
 C<sub>1-6</sub>alkanoic acid, C<sub>1-6</sub>alkylamine, CN, CO<sub>2</sub>H or CF<sub>3</sub>,  
 and  
 (f) benzyl or monosubstituted benzyl wherein the sub-  
 stituents are halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio,  
 C<sub>1-6</sub>alkanoic acid, C<sub>1-6</sub>alkylamine, CN, CO<sub>2</sub>H or CF<sub>3</sub>.  
 Within this genus there is a class of compounds wherein  
 R<sup>2</sup> is a mono- or di-substituted heteroaryl wherein heteroaryl  
 is selected from the group consisting of  
 (1) furanyl,  
 (2) diaziny,   
 (3) imidazolyl,  
 (4) isooxazolyl,  
 (5) isothiazolyl,  
 (6) oxadiazolyl,  
 (7) oxazolyl,  
 (8) pyrazolyl,  
 (9) pyridyl,

- (10) pyrrolyl,  
 (11) tetrazinyl  
 (12) tetrazolyl.  
 (13) thiadiazolyl,  
 (14) thiazolyl,  
 (15) thienyl,  
 (16) triazinyl, or  
 (17) triazolyl, and the substituents are selected from the  
 group consisting of  
 (1) hydrogen,  
 (2) halo,  
 (3) C<sub>1-4</sub>alkyl,  
 (4) C<sub>1-4</sub>alkoxy,  
 (5) C<sub>1-4</sub>alkylthio,  
 (6) CN, and  
 (7) CF<sub>3</sub>.  
 Within this class there is a sub-class of compounds  
 wherein  
 X is O;  
 Y is O;  
 R<sup>1</sup> is selected from the group consisting of  
 (a) SO<sub>2</sub>CH<sub>3</sub>, and  
 (b) SO<sub>2</sub>NH<sub>2</sub>;  
 R<sup>2</sup> is a mono- or di-substituted heteroaryl wherein heteroaryl  
 is selected from the group consisting of  
 (1) furanyl,  
 (2) diaziny,   
 (3) imidazolyl,  
 (4) oxadiazolyl,  
 (5) pyrazolyl,  
 (6) pyridyl,  
 (7) pyrrolyl,  
 (8) thiazolyl,  
 (9) thienyl, wherein the substituents are selected from the  
 group consisting of  
 (1) hydrogen,  
 (2) halo,  
 (3) methyl,  
 (4) methoxy, and  
 (5) CF<sub>3</sub>;  
 R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN,  
 C<sub>1-4</sub>fluoroalkyl, F, mono- or di-substituted phenyl, mono  
 or di-substituted benzyl, mono- or di-substituted  
 heteroaryl, mono or di-substituted heteroarylmethyl,  
 wherein the substituents are selected from the group  
 consisting of  
 (1) hydrogen,  
 (2) halo,  
 (3) C<sub>1-3</sub>alkyl,  
 (4) C<sub>1-3</sub>alkoxy,  
 (5) C<sub>1-3</sub>alkylthio,  
 (6) CN, and  
 (7) CF<sub>3</sub>;  
 R<sup>4</sup> is  
 (a) hydrogen  
 (b) C<sub>1-3</sub>alkyl,  
 (c) C<sub>1-3</sub>alkoxy,  
 (d) C<sub>1-3</sub>alkylthio, and  
 (e) —OH; and  
 R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are  
 connected form a carbonyl.

Within this sub-class there is a group of compounds wherein

X is O;

Y is O;

R<sup>1</sup> is selected from the group consisting of

(a) SO<sub>2</sub>CH<sub>3</sub>, and

(b) SO<sub>2</sub>NH<sub>2</sub>;

R<sup>2</sup> is a mono- or di-substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) furanyl,

(2) diaziny,

(3) imidazolyl,

(4) oxadiazolyl,

(5) pyrazolyl,

(6) pyridyl,

(7) thiazolyl,

(8) thienyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) Cl or F,

(3) methyl,

(4) methoxy, and

(5) CF<sub>3</sub>;

R<sup>3</sup> is hydrogen or C<sub>1-3</sub> alkyl;

R<sup>4</sup> is hydrogen or C<sub>1-3</sub> alkyl;

R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are connected form a carbonyl.

Within the above embodiment there is another genus wherein

X is selected from the group consisting of

(a) CH<sub>2</sub>, and

(b) O, Y is selected from the group consisting of (a) CH<sub>2</sub>, and (b) O,

R<sup>1</sup> is selected from the group consisting of

(a) SO<sub>2</sub>CH<sub>3</sub>,

(b) SO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>, and

(c) S(O)(NH)NH<sub>2</sub>;

R<sup>2</sup> is C<sub>1-6</sub>alkyl,

R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1-4</sub>fluoroalkyl, F, CON(R<sup>7</sup>)<sub>2</sub>, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-4</sub>alkyl,

(4) C<sub>1-4</sub>alkoxy,

(5) C<sub>1-4</sub>alkylthio,

(6) CN,

(7) CF<sub>3</sub>,

(8) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH, and

R<sup>4</sup> is

(a) hydrogen

(b) C<sub>1-6</sub>alkyl,

(c) C<sub>1-6</sub>alkoxy,

(d) C<sub>1-6</sub>alkylthio,

(e) —OH,

(f) —OCOR<sup>7</sup>,

(g) —SCOR<sup>7</sup>,

(h) —OCO<sub>2</sub>R<sup>8</sup>, and

(i) —SCO<sub>2</sub>R<sup>8</sup>,

or R<sup>3</sup> and R<sup>4</sup> together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R<sup>5</sup> and R<sup>6</sup> are each independently selected from the group consisting of

(a) hydrogen, and

(b) C<sub>1-6</sub>alkyl,

or R<sup>5</sup> and R<sup>6</sup> together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

each R<sup>7</sup> is independently selected from the group consisting of

(a) hydrogen,

(b) C<sub>1-4</sub>alkyl,

(c) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>, and

(d) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>

each R<sup>8</sup> is independently selected from the group consisting of

(a) C<sub>1-4</sub>alkyl,

(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>, and (c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>;

R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are connected form a carbonyl;

R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of

(a) hydrogen

(b) C<sub>1-6</sub>alkyl,

(c) C<sub>1-6</sub>alkanoic acid,

(d) C<sub>1-6</sub>alkyl amine,

(e) phenyl or monosubstituted phenyl wherein the substituents are halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, C<sub>1-6</sub>alkanoic acid, C<sub>1-6</sub>alkylamine, CN, CO<sub>2</sub>H or CF<sub>3</sub>, and

(f) benzyl or monosubstituted benzyl wherein the substituents are halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, C<sub>6</sub>alkanoic acid, C<sub>1-6</sub>alkylamine, CN, CO<sub>2</sub>H or CF<sub>3</sub>.

Within this genus there is a sub-genus of compounds wherein

X is O;

Y is O;

R<sup>1</sup> is selected from the group consisting of

(a) SO<sub>2</sub>CH<sub>3</sub>,

(b) S(O)<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>, and

(c) S(O)(NH)NH<sub>2</sub>;

R<sup>2</sup> is C<sub>1-4</sub>alkyl,

R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN, C<sub>1-4</sub>fluoroalkyl, F, CON(R<sup>7</sup>)<sub>2</sub>, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C<sub>1-4</sub>alkyl,

(4) C<sub>1-4</sub>alkoxy,

(5) C<sub>1-4</sub>alkylthio,  
 (6) CN,  
 (7) CF<sub>3</sub>,  
 (8) —C(R<sup>5</sup>)(R<sup>6</sup>)—OH, and  
 R<sup>4</sup> is  
 (a) hydrogen  
 (b) C<sub>1-6</sub>alkyl,  
 (c) C<sub>1-6</sub>alkoxy,  
 (d) C<sub>1-6</sub>alkylthio,  
 (e) —OH,  
 (f) —OCOR<sup>7</sup>,  
 (g) —SCOR<sup>7</sup>,  
 (h) —OCO<sub>2</sub>R<sup>8</sup>, and  
 (i) —SCO<sub>2</sub>R<sup>8</sup>,  
 or R<sup>3</sup> and R<sup>4</sup> together with the carbon to which they are  
 attached form a saturated monocyclic carbon ring of 3, 4,  
 5, 6 or 7 atoms;  
 R<sup>5</sup> and R<sup>6</sup> are each independently selected from the group  
 consisting of  
 (a) hydrogen, and  
 (b) C<sub>1-6</sub>alkyl,  
 or R<sup>5</sup> and R<sup>6</sup> together with the atom to which they are  
 attached form a saturated monocyclic ring of 3, 4, 5, 6  
 or 7 atoms;  
 each R<sup>7</sup> is independently selected from the group consisting  
 of  
 (a) hydrogen,  
 (b) C<sub>1-4</sub>alkyl,  
 (c) phenyl or monosubstituted phenyl wherein the sub-  
 stituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy,  
 C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>, and  
 (d) benzyl or monosubstituted benzyl wherein the sub-  
 stituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy,  
 C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>,  
 each R<sup>8</sup> is independently selected from the group consisting  
 of  
 (a) C<sub>1-4</sub>alkyl,  
 (b) phenyl or monosubstituted phenyl wherein the sub-  
 stituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy,  
 C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>, and  
 (c) benzyl or monosubstituted benzyl wherein the sub-  
 stituents may be halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy,  
 C<sub>1-4</sub>alkylthio, CN, or CF<sub>3</sub>;  
 R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are  
 connected form a carbonyl;  
 R<sup>16</sup> and R<sup>17</sup> are independently selected from the group  
 consisting of  
 (a) hydrogen  
 (b) C<sub>1-6</sub>alkyl,  
 (c) C<sub>1-6</sub>alkanoic acid,  
 (d) C<sub>1-6</sub>alkyl amine,  
 (e) phenyl or monosubstituted phenyl wherein the sub-  
 stituents are halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio,  
 C<sub>1-6</sub>alkanoic acid, C<sub>1-6</sub>alkylamine, CN, COOH or CF<sub>3</sub>,  
 and  
 (f) benzyl or monosubstituted benzyl wherein the sub-  
 stituents are halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio,  
 C<sub>1-6</sub>alkanoic acid, C<sub>1-6</sub>alkylamine, CN, COOH or CF<sub>3</sub>.  
 Within this sub-genus there is a class of compounds  
 wherein  
 X is O;  
 Y is O;

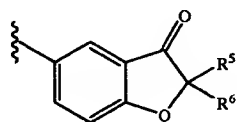
R<sup>1</sup> is selected from the group consisting of  
 (a) SO<sub>2</sub>CH<sub>3</sub>, and  
 (b) SO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>;  
 R<sup>2</sup> is propyl or butyl,  
 R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl, CH<sub>2</sub>OR<sup>7</sup>, CN, CH<sub>2</sub>CN,  
 C<sub>1-4</sub>fluoroalkyl, F, mono- or di-substituted phenyl, mono  
 or di-substituted benzyl, mono- or di-substituted  
 heteroaryl, mono or di-substituted heteroarylmethyl,  
 wherein the substituents are selected from the group  
 consisting of  
 (1) hydrogen,  
 (2) halo,  
 (3) C<sub>1-3</sub>alkyl,  
 (4) C<sub>1-3</sub>alkoxy,  
 (5) C<sub>1-3</sub>alkylthio,  
 (6) CN, and  
 (7) CF<sub>3</sub>;  
 R<sup>4</sup> is  
 (a) hydrogen  
 (b) C<sub>1-3</sub>alkyl,  
 (c) C<sub>1-3</sub>alkoxy,  
 (d) C<sub>1-3</sub>alkylthio, and  
 (e) —OH; and  
 R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are  
 connected form a carbonyl. Preferred R<sup>1</sup> is SO<sub>2</sub>CH<sub>3</sub> or R<sup>1</sup>  
 is SO<sub>2</sub>NH<sub>2</sub>.  
 Within this class there is a sub-class of compounds  
 wherein  
 X is O;  
 Y is O;  
 R<sup>1</sup> is selected from the group consisting of  
 (a) SO<sub>2</sub>CH<sub>3</sub>, and  
 (b) SO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>;  
 R<sup>2</sup> is propyl or butyl,  
 R<sup>3</sup> is hydrogen or C<sub>1-3</sub> alkyl;  
 R<sup>4</sup> is hydrogen or C<sub>1-3</sub> alkyl;  
 R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are  
 connected form a carbonyl.  
 Within this sub-class there is a group of compounds  
 wherein  
 X is O;  
 Y is O;  
 R<sup>1</sup> is selected from the group consisting of  
 (a) SO<sub>2</sub>CH<sub>3</sub>, and  
 (b) SO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup>;  
 R<sup>2</sup> is isopropyl,  
 R<sup>3</sup> is methyl or ethyl;  
 R<sup>4</sup> is methyl or ethyl; and  
 R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are  
 connected form a carbonyl.  
 For purposes of this specification heteroaryl as in R<sup>2</sup>, R<sup>3</sup>,  
 or R<sup>15</sup> is intended to include, but is not limited to optionally  
 mono- or di-substituted  
 (1) furanyl,  
 (2) diaziny,   
 (3) imidazolyl,  
 (4) isooxazolyl,  
 (5) isothiazolyl,  
 (6) oxadiazolyl,  
 (7) oxazolyl,  
 (8) pyrazolyl,  
 (9) pyridyl,

17

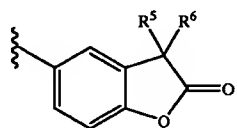
- (10) pyrrolyl,
- (11) tetrazinyl
- (12) tetrazolyl.
- (13) thiadiazolyl,
- (14) thiazolyl,
- (15) thienyl,
- (16) triazinyl, or
- (17) triazolyl.

Similarly, for purposes of this specification cyclic groups such as a heterocycloalkyl or benzocarbocycle or benzoheterocycle such as in  $R^2$  or  $R^{15}$  is intended to include, but is not limited to optionally mono- or di-substituted

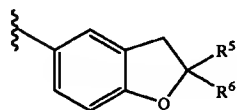
- (1) tetrahydrothiopyranyl,
- (2) thiomorpholinyl,
- (3) pyrrolidinyl,
- (4) hexahydroazepinyl,
- (5) indanyl,
- (6) tetralinyl,
- (7) indolyl,
- (8) benzofuranyl,
- (9) benzothieryl,
- (10) benzimidazolyl,
- (11) benzothiazolyl,



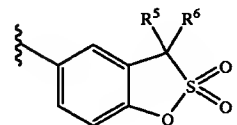
(12)



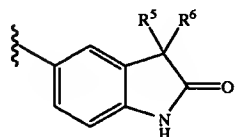
(13)



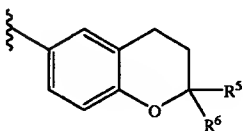
(14)



(15)



(16)

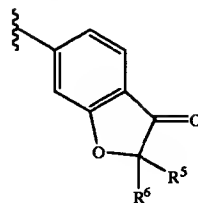


(17)

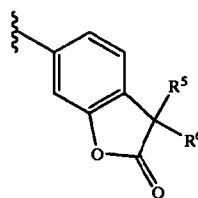
18

-continued

(18)

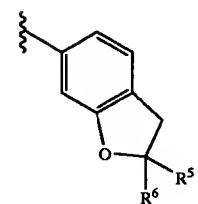


5



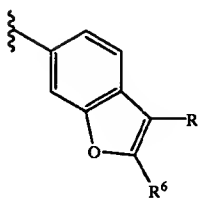
10

(19)



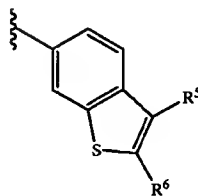
15

(20)



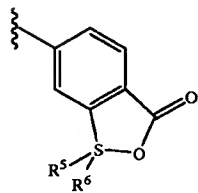
25

(21)



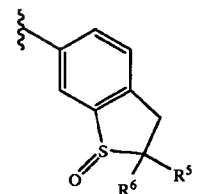
40

(22)



50

(23)

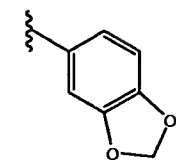


65

(24)

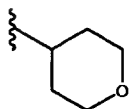
19

-continued



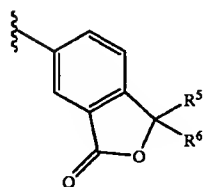
(25)

5



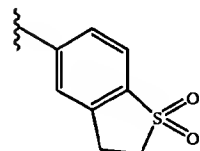
(26)

10



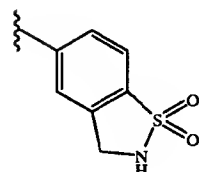
(27)

15



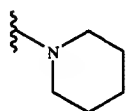
(28)

20



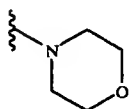
(29)

25



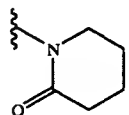
(30)

30



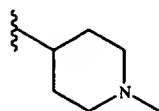
(31)

35



(32)

40



(33)

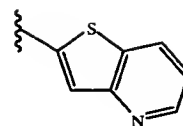
45

50

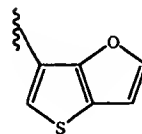
55

60

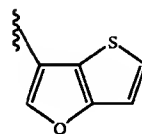
20



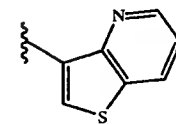
(1)



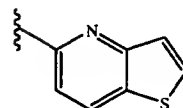
(2)



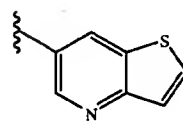
(3)



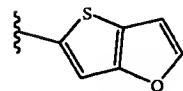
(4)



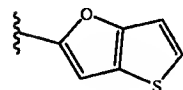
(5)



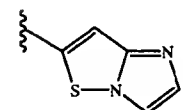
(6)



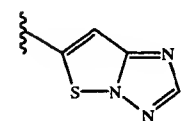
(7)



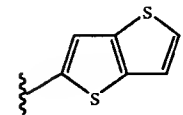
(8)



(9)



(10)

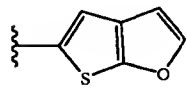
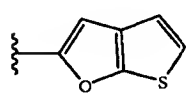
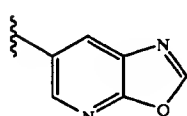
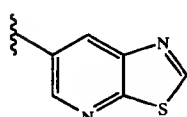
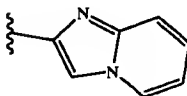
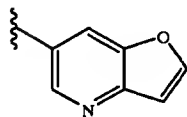
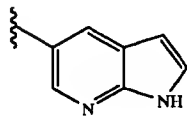
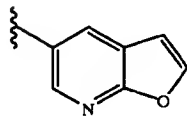
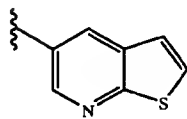
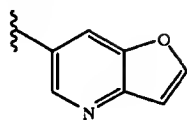


(11)

Similarly, for purposes of this specification bicyclic heteroaryl as in R<sup>2</sup> is intended to include, but is not limited to optionally mono- or di-substituted

65

-continued



One preferred genus is directed to compounds of Formula I wherein  $R^9$  and  $R^{10}$  together with the carbon atom to which they are attached form a carbonyl (ie  $R^9$  and  $R^{10}$  together form a double bonded O).

Another preferred genus is directed to compounds of Formula I wherein Y is O.

Another preferred genus is directed to compounds of Formula I wherein X is O.

- (12) Another preferred genus is directed to compounds of Formula I wherein  $R^9$  and  $R^{10}$  together with the carbon to which they are attached from a carbonyl;

Y is O; and

- 5 X is O.

- (13) Another preferred genus is directed to compounds of Formula I wherein

$R^2$  is a mono-, di- or tri-substituted phenyl wherein the substituents are selected from the group consisting of

- 10 (a) hydrogen,

(b) halo,

(c) CN,

- (14) (d)  $CF_3$ , and

(e)  $C_{1-4}$  alkyl.

- 15 Another preferred genus is directed to compounds of Formula I wherein

$R^2$  is mono-, di-, or tri-substituted pyridyl wherein the substituents are selected from the group consisting of

- (15) (a) hydrogen,

20 (b) halo,

(c)  $C_{1-4}$  alkyl,

(d)  $C_{1-4}$  alkoxy

(e)  $C_{1-4}$  alkythio,

(f) CN, and

- (16) 25 (g)  $CF_3$ .

Another preferred genus is directed to compounds of Formula I wherein

$R^9$  and  $R^{10}$  together with the carbon to which they are attached from a carbonyl;

- 30 Y is O;

- (17) X is O, and

$R^2$  is a mono-, di- or tri-substituted phenyl wherein the substituents are selected from the group consisting of

- 35 (a) hydrogen,

(b) halo,

- (18) (c) CN,

(d)  $CF_3$ , and

- (e)  $C_{1-4}$  alkyl.

- 40 Another preferred genus is directed to compounds of Formula I wherein

$R^9$  and  $R^{10}$  together with the carbon to which they are attached from a carbonyl,

- (19) Y is O,

- 45 X is O, and

R<sup>2</sup> is a mono-, di-, or

- (20) tri-substituted pyridyl wherein the substituents are selected from the group consisting of

- 50 (a) hydrogen,

(b) halo,

- (c)  $C_{1-4}$  alkyl,

- (21) (d)  $C_{1-4}$  alkoxy,

(e)  $C_{1-4}$  alkythio,

- 55 (f) CN, and

- (g)  $CF_3$ .

Another preferred genus is directed to compounds of Formula I wherein

- 60  $R^2$  is a mono- or di-substituted phenyl, naphthyl, heteroaryl, benzoheterocycle, benzocarbocycle or bicyclic heteroaryl, wherein the substituents are selected from the group consisting of

- (a) hydrogen,

- 65 (b) halo,

(d)  $C_{1-4}$  alkyl,

(e)  $C_{1-4}$  alkoxy,



(f) C<sub>1-4</sub> alkythio,

(g) CN, and

(h) CF<sub>3</sub>.

Another preferred genus is directed to compounds of Formula I wherein

R<sup>9</sup> and R<sup>10</sup> together with the carbon to which they are attached from a carbonyl, and

Y is CH<sub>2</sub>.

Another preferred genus is directed to compounds of Formula I wherein

R<sup>3</sup> is hydrogen or C<sub>1-10</sub> alkyl, particularly a propyl or butyl.

Another preferred genus is directed to compounds of Formula I wherein

R<sup>3</sup> is substituted pyridine, particularly a 3-pyridine.

Another preferred genus is directed to compounds of Formula I wherein R<sup>1</sup> is methyl sulfonyl.

Another preferred genus is directed to compounds of formula I wherein R16 and R17 are each hydrogen.

In another aspect the invention also encompasses a pharmaceutical composition for treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent comprising:

a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

In another aspect the invention also encompasses a pharmaceutical composition for treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:

a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

In another aspect the invention also encompasses a method of treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent comprising:

administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

In another aspect the invention also encompasses a method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:

administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of formula I.

In another aspect the invention also encompasses the use of a compound of formula I or a pharmaceutical composition in the manufacture of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

The invention is illustrated by the compounds of the Examples disclosed herein as well as the compounds of Table I.

#### 1) Definitions

The following abbreviations have the indicated meanings:

AA=arachidonic acid

Ac=acetyl

AIBN=2,2'-azobisisobutyronitrile

Bn=benzyl

CHO=chinese hamster ovary

CMC=1-cyclohexyl-3-(2-morpholinoethyl) carbodiimidemetho-p-toluenesulfonate

COX=cyclooxygenase

DBU=diazahicyclo[5.4.0]undec-7-ene

DMAp=4-(dimethylamino)pyridine

DMF=N,N-dimethylformamide

DMSO=dimethyl sulfoxide

Et<sub>3</sub>N=triethylamine

HBSS=Hanks balanced salt solution

HEPES=N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]

5 HWB=human whole blood

IPA=isopropyl alcohol

KHMDS=potassium hexamethyldisilazane

LDA=lithium diisopropylamide

LPS=lipopolysaccharide

mCPBA=metachloro perbenzoic acid

10 MMPP=magnesium monoperoxyphthalate

Ms=methanesulfonyl=mesyl

MsO=methanesulfonate=mesylate

NBS=N-bromosuccinimide

NCS=N-chlorosuccinimide

15 NIS=N-iodosuccinimide

NSAID=non-steroidal anti-inflammatory drug

ODCB=o-dichlorobenzene

Oxone®=potassium peroxymonosulfate

PCC=pyridinium chlorochromate

20 PDC=pyridinium dichromate

r.t.=room temperature

rac.=racemic

Tf=trifluoromethanesulfonyl=triflyl

TFAA=trifluoroacetic anhydride

25 TfO=trifluoromethanesulfonate=triflate

THF=tetrahydrofuran

TLC=thin layer chromatography

TMPPD=N,N,N',N'-tetramethyl-p-phenylenediamine

Ts=p-toluenesulfonyl=tosyl

TsO=p-toluenesulfonate=tosylate

30 Tz=1H (or 2H)-tetrazol-5-yl

SO<sub>2</sub>Me=methyl sulfone (also SO<sub>2</sub>CH<sub>3</sub>)

SO<sub>2</sub>NH<sub>2</sub>=sulfonamide

35 Alkyl group abbreviations	Dose Abbreviations
Me = methyl	bid = bis in die = twice daily
Et = ethyl	qid = quater in die = four times a day
n-Pr = normal propyl	id = ter in die = three times a day
i-Pr = isopropyl	
40 n-Bu = normal butyl	
i-Bu = isobutyl	
s-Bu = secondary butyl	
t-Bu = tertiary butyl	
c-Pr = cyclopropyl	
c-Bu = cyclobutyl	
c-Pen = cyclopentyl	
45 c-Hex = cyclohexyl	

For purposes of this specification "Alkyl" means linear branched and cyclic structures, and combinations thereof, containing the indicated number of carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl-4-propylnonyl, cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1-hicyclo[4.4.0]decyl and the like.

For purposes of this specification "Fluoro alkyl" means alkyl groups in which one or more hydrogen is replaced by fluorine. Examples are —CF<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>F, —CH<sub>2</sub>CF<sub>3</sub>, c-Pr-F<sub>3</sub>, c-Hex-F<sub>11</sub> and the like.

For purposes of this specification "Alkoxy" means alkoxy groups of the indicated number of carbon atoms of a straight, branched, or cyclic configuration. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

For purposes of this specification "Alkylthio" means alkylthio groups of the indicated number of carbon atoms of

a straight, branched or cyclic configuration. Examples of alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies  $\text{—SCH}_2\text{CH}_2\text{CH}_3$ .

For purposes of this specification "Halo" means F, Cl, Br, or I.

Exemplifying the invention are Examples hereinunder which include:

- (1) 3-(3,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (2) 3-(3-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (3) 3-(3,5-Difluorophenoxy)-5,5-dimethyl-4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (4) 3-Phenoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (5) 3-(2,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (6) 3-(4-Chlorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (7) 3-(3,4-Dichlorophenoxy)-5,5-dimethyl-4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (8) 3-(4-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (9) 3-(4-Fluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (10) 3-(3,5-Difluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (11) 3-Phenylthio-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (12) 3-(N-Phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (13) 3-(N-Methyl-N-phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (14) 3-Cyclohexyloxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (15) 3-Phenylthio-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (16) 3-Benzyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (17) 3-(3,4-Difluorophenylhydroxymethyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (18) 3-(3,4-Difluorobenzoyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (19) 3-Benzoyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (20) 4-(4-(Methylsulfonyl)phenyl)-3-phenoxy-1-oxaspiro[4.4]non-3-en-2-one,
- (21) 4-(4-(Methylsulfonyl)phenyl)-3-phenylthio-1-oxaspiro[4.4]non-3-en-2-one,
- (22) 4-(2-Oxo-3-phenylthio-1-oxa-spiro[4.4]non-3-en-4-yl) benzenesulfonamide,
- (23) 3-(4-Fluorobenzyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (24) 3-(3,4-Difluorophenoxy)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (25) 3-(5-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (26) 3-(2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (27) 3-(6-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (28) 3-(3-Isoquinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
- (29) 3-(4-(Methylsulfonyl)phenyl)-2-phenoxy-cyclopent-2-enone, and
- (30) 3-(4-(Methylsulfonyl)phenyl)-2-(3,4-difluorophenoxy)-cyclopent-2-enone.

Further exemplifying the invention are

- (a) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(5-bromopyridin-2-yloxy)-5H-furan-2-one, and
- (b) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one, or

a pharmaceutically acceptable salt thereof.

Also see Examples 1-205.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising:

administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, such as arginine, betaine, caffeine, choline, N,N-dihenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like, and basic ion exchange resins.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including

rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, 5 bumps, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. Compound I may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile 15 prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, and for the prevention of bone loss (treatment of osteoporosis) and for the treatment of glaucoma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), Compound I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated 25 such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, Compound I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H<sub>2</sub>-antagonist, aluminum or magnesium hydroxide, 35 simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephedrine, naphazoline, xylometazoline, propylhexedrine, or levodexyephedrine; an antitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a prostaglandin including misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effective amount of the compound of Formula I, optionally co-administered with one or more 55 of such ingredients as listed immediately above.

For the treatment of any of these cyclooxygenase mediated diseases Compound I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats,

horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of 15 sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or 25 acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. 50 The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as

liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of

body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

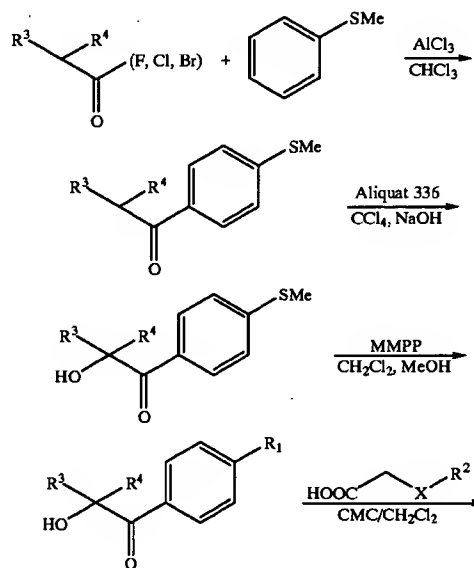
The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention can be prepared according to the following methods

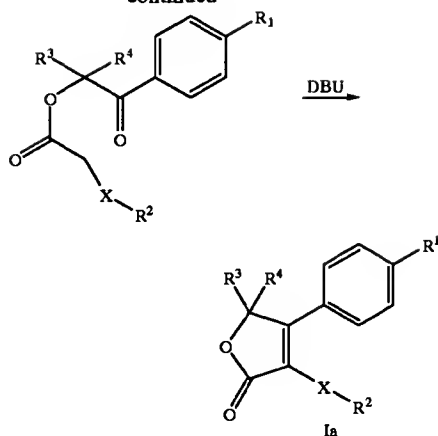
#### Method A

An appropriately substituted acid halide is reacted with thioanisole in a solvent such as chloroform in the presence of a Lewis acid such as aluminum chloride to afford a ketone which is then hydroxylated with base such as aqueous sodium hydroxide in a solvent such as carbon tetrachloride with a phase transfer agent such as Aliquat 336. Then treatment with an oxidizing agent such as MMPP in solvents such as  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , affords a sulfone which is reacted with an appropriately substituted acetic acid in a solvent such as  $\text{CH}_2\text{Cl}_2$  in the presence of an esterifying agent such as CMC and DMAP and then treated with DBU to afford lactone Ia.



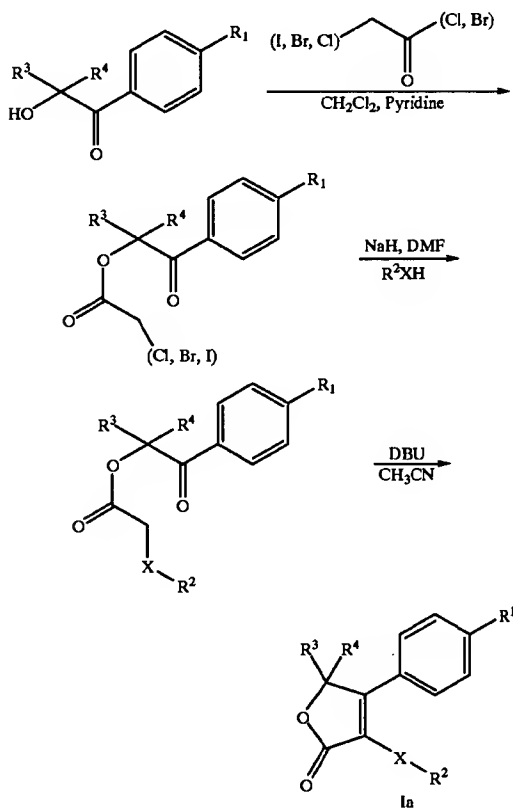
31

-continued



## Method B

An appropriately substituted hydroxyketone is acylated with an appropriately substituted acid halide in a solvent such as dichloromethane in the presence of a base such as pyridine. The ester obtained is then reacted with an appropriately substituted nucleophile  $\text{R}^2\text{XH}$  in a solvent such as DMF and with a base such as sodium hydride, then treatment with DBU in a solvent such as acetonitrile affords lactone Ia.



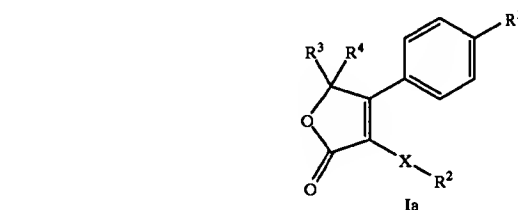
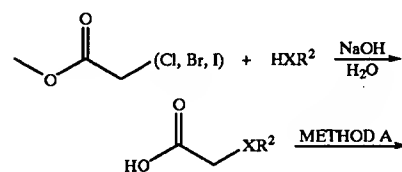
32

-continued

$R^1 = \text{SO}_2\text{Me}$   
 $X = \text{O}, \text{S}, \text{NR}^{15}$

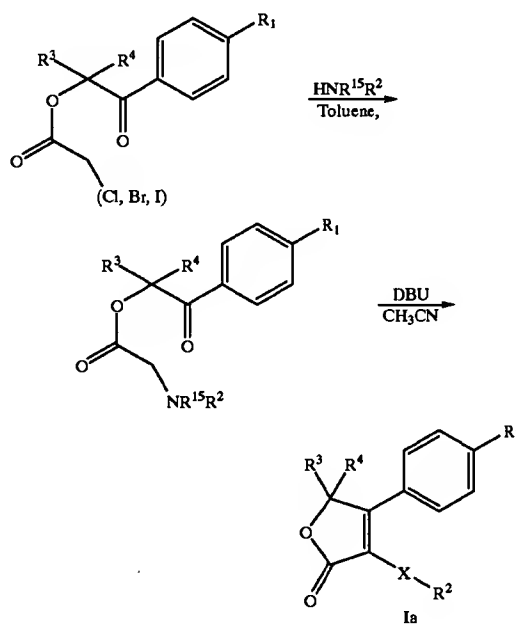
## Method C

A halo ester of acetic acid is coupled with an appropriately substituted nucleophile in water with sodium hydroxide to give an appropriately substituted acetic acid which is then reacted as in method A to afford lactone Ia.



## Method D

A halo ester is reacted with an appropriately substituted amine  $\text{R}^2\text{R}^{15}\text{NH}$  in a solvent such as toluene to give an intermediate which is then reacted with DBU in a solvent such as acetonitrile to afford lactone Ia.

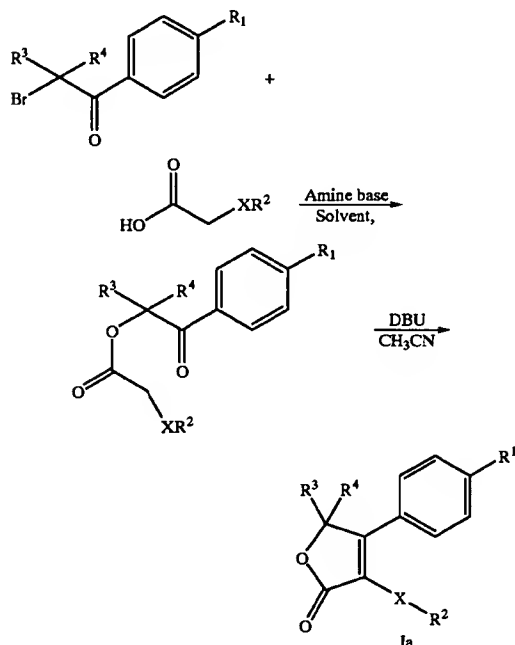


## Method E

An appropriately substituted bromoketone is reacted with an appropriately substituted acid in a solvent such as ethanol or acetonitrile in the presence of a base such as diisopropyl-

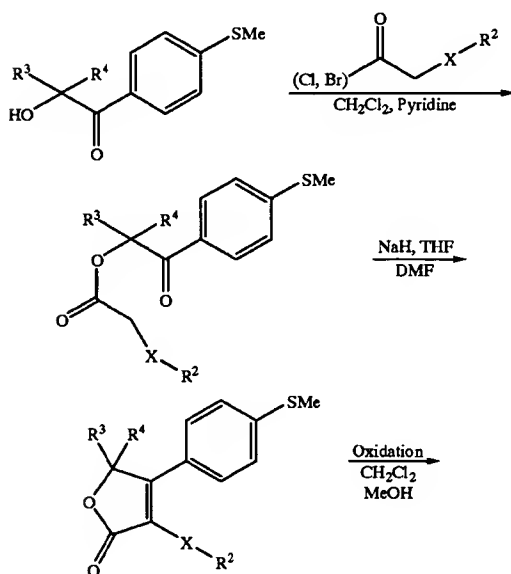
## 33

diethylamine or triethylamine to afford an ester which is then treated with DBU in a solvent such as acetonitrile to afford lactone Ia.



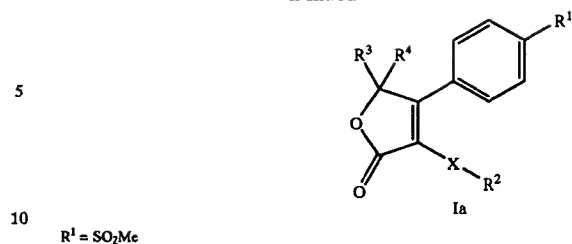
## Method F

An appropriately substituted hydroxyketone is reacted with an appropriately substituted acid halide in a solvent such as dichloromethane and with a base such as pyridine to afford an ester which is then cyclized using sodium hydride in a mixture of THF and DMF to afford a lactone. The lactone is then oxidized with an oxidizing agent such as MMPP, mCPBA or OXONE® in solvents such as dichloromethane and/or methanol to afford lactone Ia.



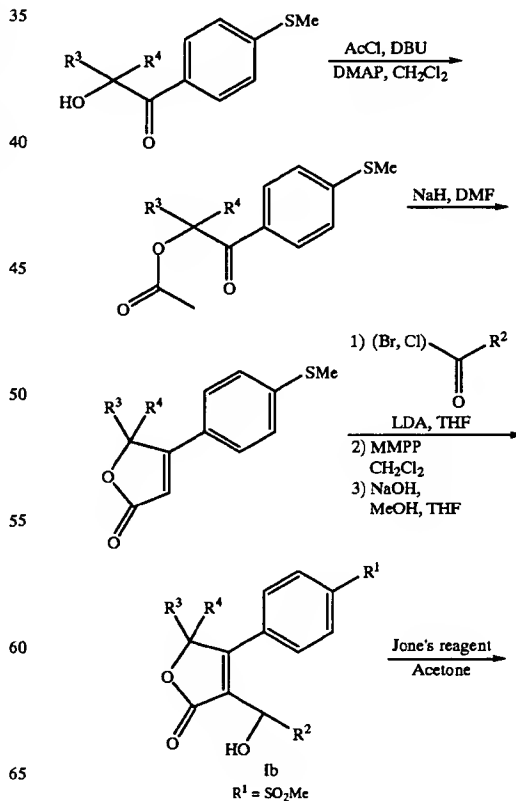
## 34

-continued



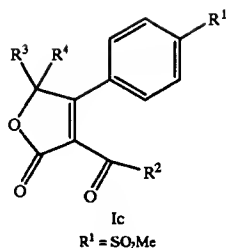
## Method G

An appropriately substituted hydroxyketone is acylated with acetyl bromide or chloride in a solvent such as dichloromethane with a base such as DBU and DMAP. Further treatment with a base such as sodium hydride in a solvent such as DMF effects cyclization to afford the 5-membered lactone. Treatment of this lactone with a base such as LDA and an appropriately substituted acid halide in a solvent such as THF, followed by oxidation with a reagent such as MMPP in solvent such as  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  and hydrolysis by a base such as NaOH in a solvent such as MeOH/THF gives an alcohol Ib which is then oxidized to lactone Ic by a reagent such as Jones' reagent in a solvent such as acetone (the initially formed ketone is reduced in the reaction and acylated, thus requiring hydrolysis and re-oxidation to obtain ketone Ic). Alternatively, alcohol Ib can be obtained by using an aldehyde  $\text{R}^2\text{CHO}$  as the electrophile instead of an acid halide.



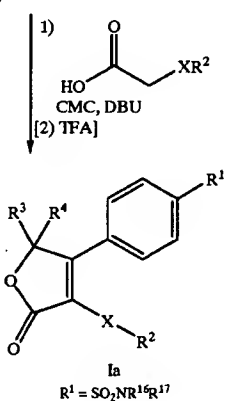
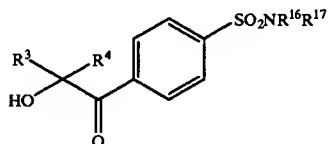
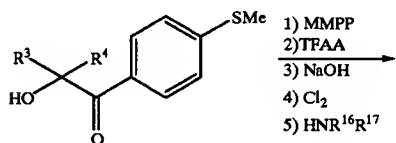
35

-continued



## Method H

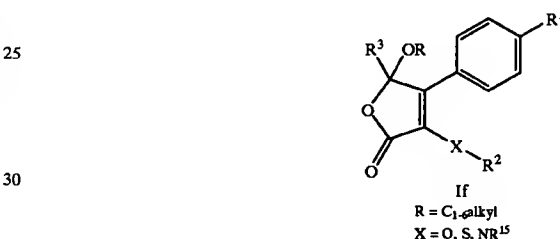
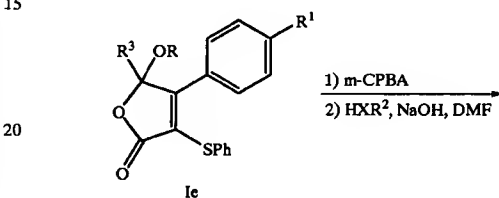
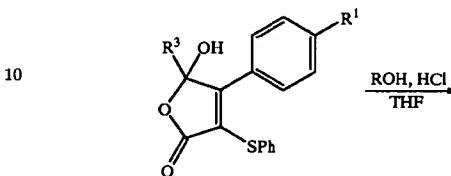
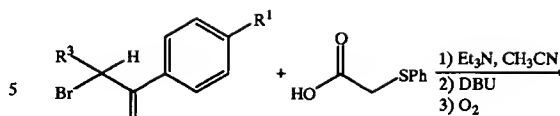
An appropriately substituted methyl sulfide is oxidized to the sulfoxide with a reagent such as MMPP in solvents such as dichloromethane and methanol followed by treatment with trifluoroacetic anhydride, then aqueous sodium hydroxide. Further treatment by Cl<sub>2</sub> in aqueous acetic acid followed by treatment by an amine affords an intermediate sulfonamide. This sulfonamide is then esterified with an appropriately substituted acid in the presence of a reagent such as CMC and further treatment with a base such as DBU affords the lactone. In the case where the amine group is protected by an acid labile group treatment with an acid such as trifluoroacetic acid in a solvent such as dichloromethane affords compound Ia.



## Method I

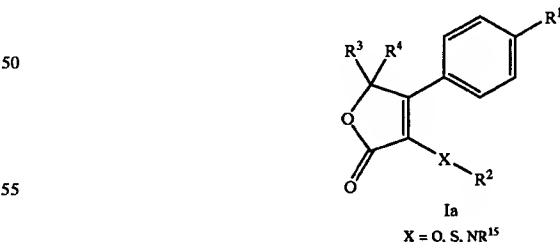
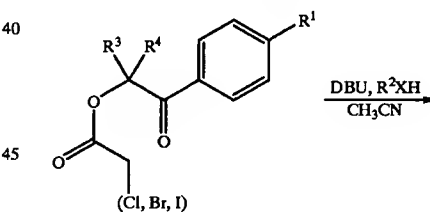
An appropriately substituted bromoketone is reacted with an appropriately substituted acid in a solvent such as acetonitrile and with a base such as Et<sub>3</sub>N. Treatment with DBU and then O<sub>2</sub> gives a hydroxy compound Id. Etherification of this hydroxy with an alcohol in a solvent such as THF and with an acid such as HCl gives Ie. By oxidation of the sulfide into a sulfone by a reagent such as m-CPBA and then displacement of this sulfone by an appropriately substituted nucleophile compound If is obtained.

36



## Method J

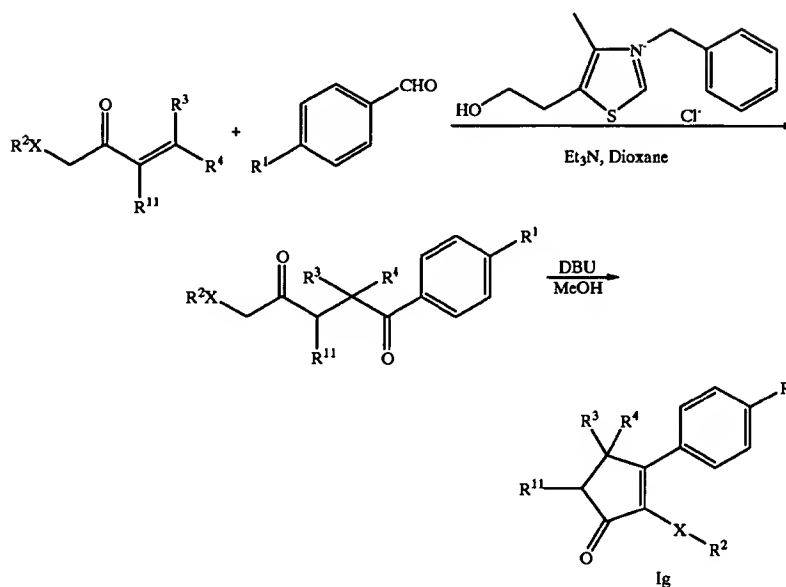
An appropriately substituted nucleophile is reacted with an appropriately substituted haloacetate in a solvent such as acetonitrile with a base such as DBU to afford compound Ia.



## Method K

An appropriately substituted vinyl ketone is coupled with an appropriately substituted benzaldehyde with a catalyst such as 3-benzyl-(2-hydroxyethyl)-4-methylthiazolium chloride in the presence of a base such as triethylamine in a solvent such as 1,4-dioxane to form a diketone. The diketone is cyclized in a solvent such as methanol with a base such as DBU to the final product Ig. When R<sup>1</sup>=SO<sub>2</sub>Me, the starting material can also be a p-methylthiobenzaldehyde, with the

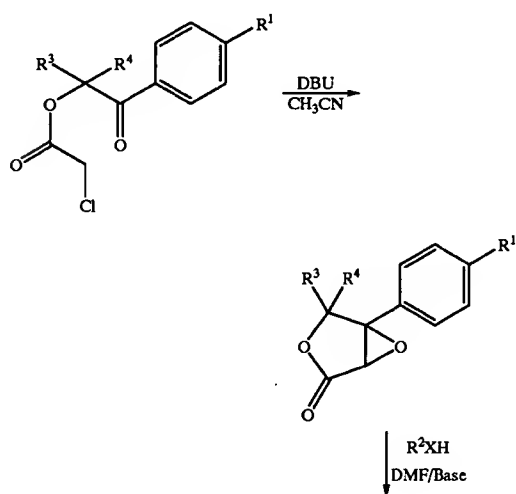
methylthio group being oxidized to SO<sub>2</sub>Me using MMPP, mCPBA or OXONE® in the last step.



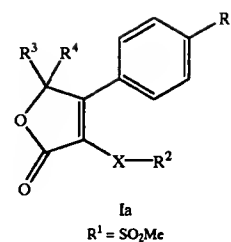
#### Method L

30

An appropriately substituted halide is reacted with a base such as DBU in a solvent such as acetonitrile to afford an epoxide which is then reacted with an appropriately substituted nucleophile in solvents such as DMF and a base to afford lactone Ia.



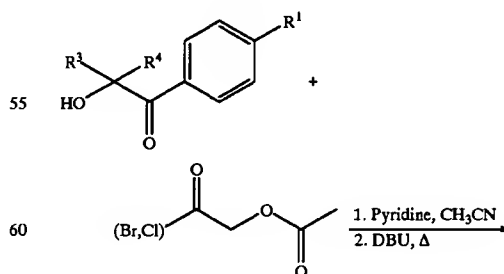
-continued



#### Method M

An appropriately substituted acid halide is reacted with an appropriately substituted hydroxyketone in the presence of a base such as pyridine in a solvent such as acetonitrile, further treatment with a base such as DBU gives an hydroxylactone. The hydroxylactone is reacted with an appropriately substituted halide in a solvent such as benzene with a reagent such as Ag<sub>2</sub>CO<sub>3</sub> to afford the lactone Ih.

50

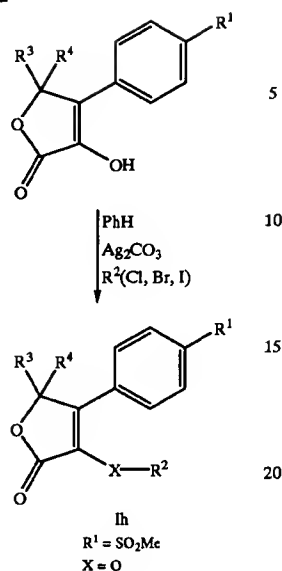


65



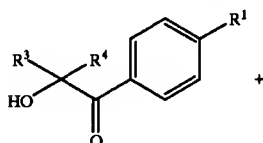
39

-continued



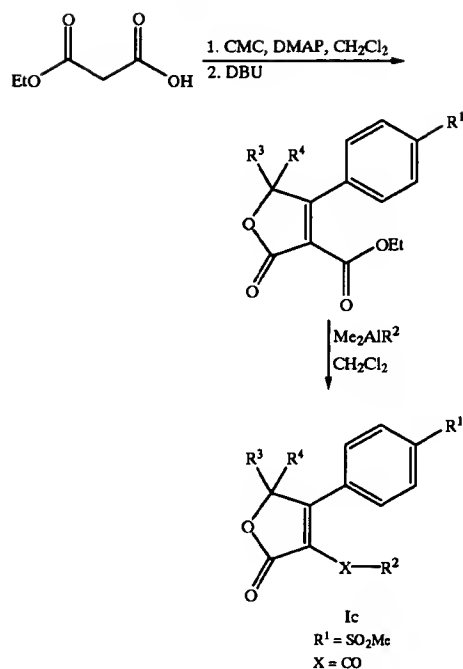
## Method N

An appropriately substituted hydroxyketone is reacted with an appropriately substituted carboxylic acid with an esterifying agent such as CMC in the presence of DMAP in a solvent such as CH<sub>2</sub>Cl<sub>2</sub>, followed by treatment with a base such as DBU to afford a lactone ester. This lactone ester is then reacted with a reagent such as the one formed with piperidine and trimethylaluminum to afford the lactone 1c.



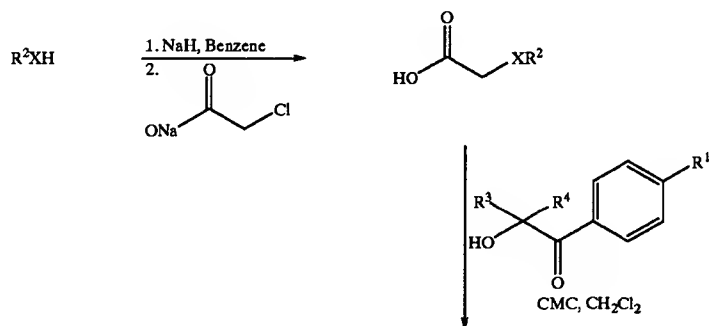
40

-continued

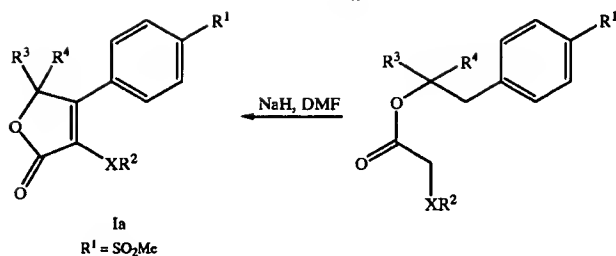


## Method O

An appropriately substituted nucleophile such as pentan-3-ol is treated with a base such as sodium hydride in a solvent such as benzene and then reacted with an electrophile such as sodium chloroacetate to afford an acid. This acid is then reacted with an appropriately substituted hydroxyketone with an esterifying reagent such as CMC in a solvent such as dichloromethane to give an ester which is cyclized upon treatment with a base such as sodium hydride in a solvent such as DMF to afford lactone 1a.



-continued



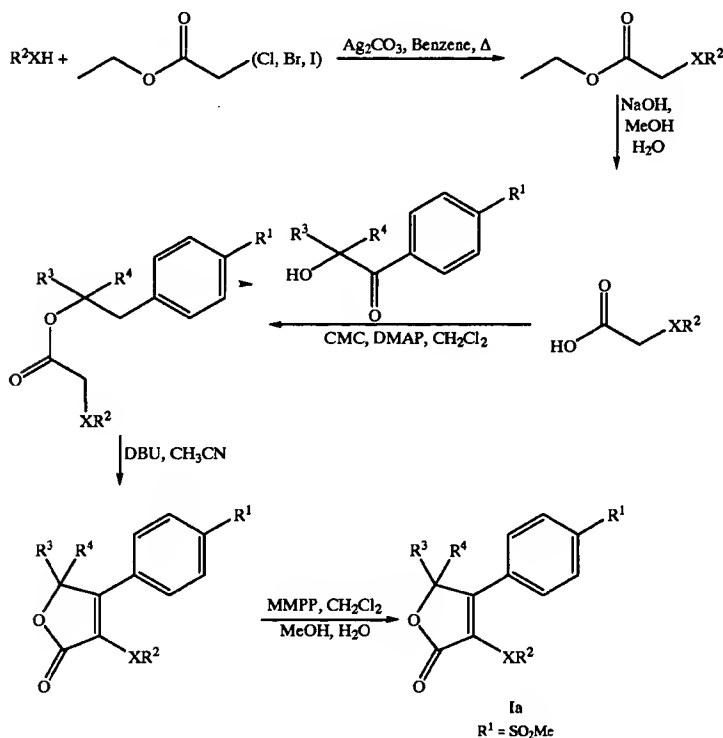
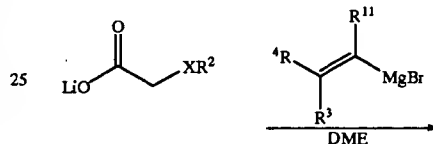
## Method P

An appropriately substituted nucleophile is reacted with an appropriately substituted haloacetate alkaline salt (such as sodium) in a solvent such as benzene and with a reagent such as Ag<sub>2</sub>CO<sub>3</sub> to give an ester which is then hydrolyzed with a reagent such as NaOH in solvents such as water and methanol to give an acid. The acid is then esterified with an appropriately substituted hydroxyketone with reagents such as CMC and DMAP in a solvent such as dichloromethane to give an ester which is then cyclized with a base such as DBU in a solvent such as CH<sub>3</sub>CN to afford a lactone. The sulfide is then oxidized with a reagent such as MMPP in solvents such as CH<sub>2</sub>Cl<sub>2</sub>, MeOH and water to afford lactone Ia.

## 15 Method Q

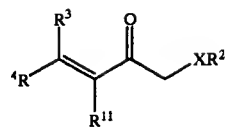
An appropriately substituted acetic acid salt is reacted with a nucleophile such as vinyl magnesium bromide in a solvent such as DME to afford a ketone, which is then reacted as in method K to afford cyclopentone Ig.

20

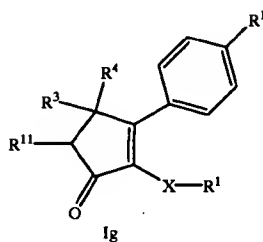


43

-continued



Method K



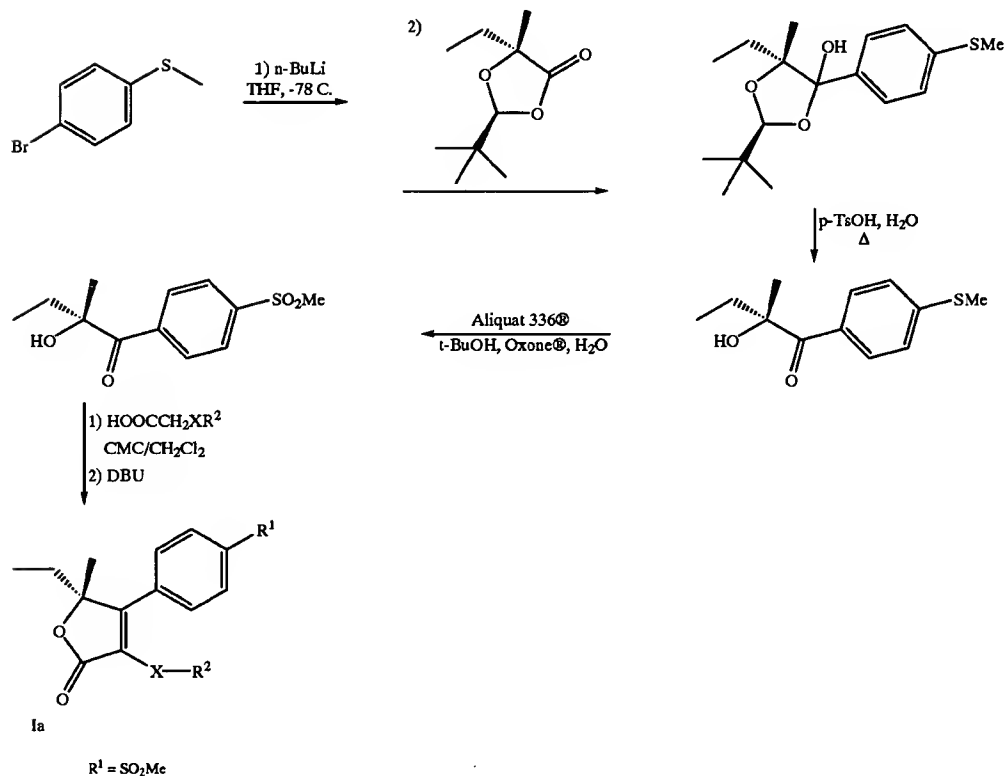
Ig

Method R

44

4-Bromothiobanisole is reacted with a base such as n-BuLi in a solvent such as THF to form the corresponding lithium reagent which is then reacted with an appropriately substituted lactone (*Tetrahedron*, 1984, 40, 1313) to give a hemiketal. The acetal is then cleaved with an acidic such as p-TsOH in a solvent such as water to give a hydroxyketone. The sulfide is then oxidized with a reagent such as Oxone®, in the presence of a phase transfer reagent such as Aliquat 336® in solvents such as t-BuOH and water to give a sulfone. The hydroxyketone is then esterified with an appropriately substituted acetic acid with reagents such as CMC and DMAP in a solvent such as CH<sub>2</sub>Cl<sub>2</sub> to give an intermediate ester which is cyclized with a base such as DBU to give lactone Im.

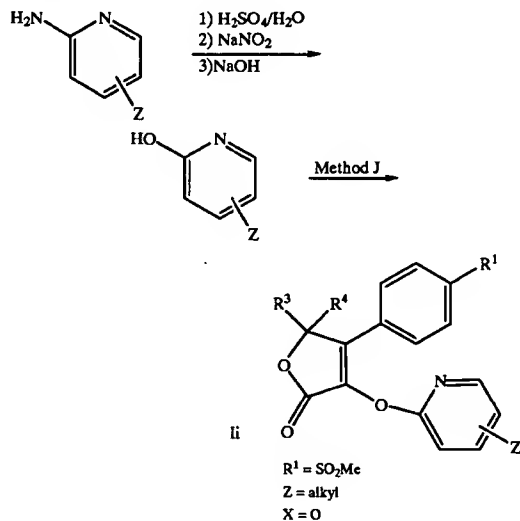
20



45

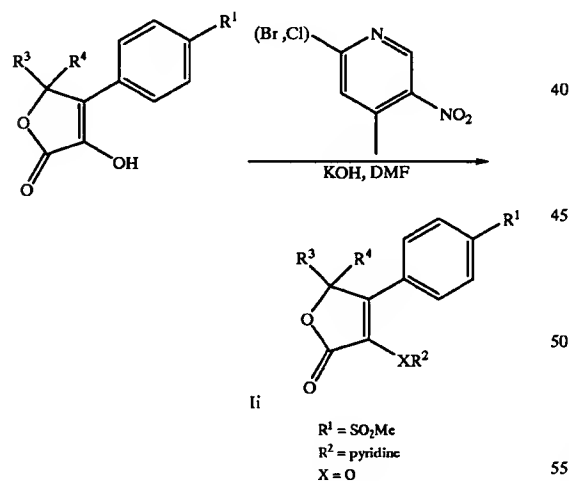
## Method S

An appropriately substituted aminopyridine is diazotized with  $\text{NaNO}_2$  in an acid such as  $\text{H}_2\text{SO}_4$  in water, followed by neutralization with  $\text{NaOH}$  affords an hydroxypyridine which is reacted following the method J.



## Method T

An appropriately substituted hydroxylactone is treated with a base such as  $\text{KOH}$  in a solvent such as  $\text{DMF}$ , followed by treatment with an appropriately substituted halopyridine afford lactone **li**.

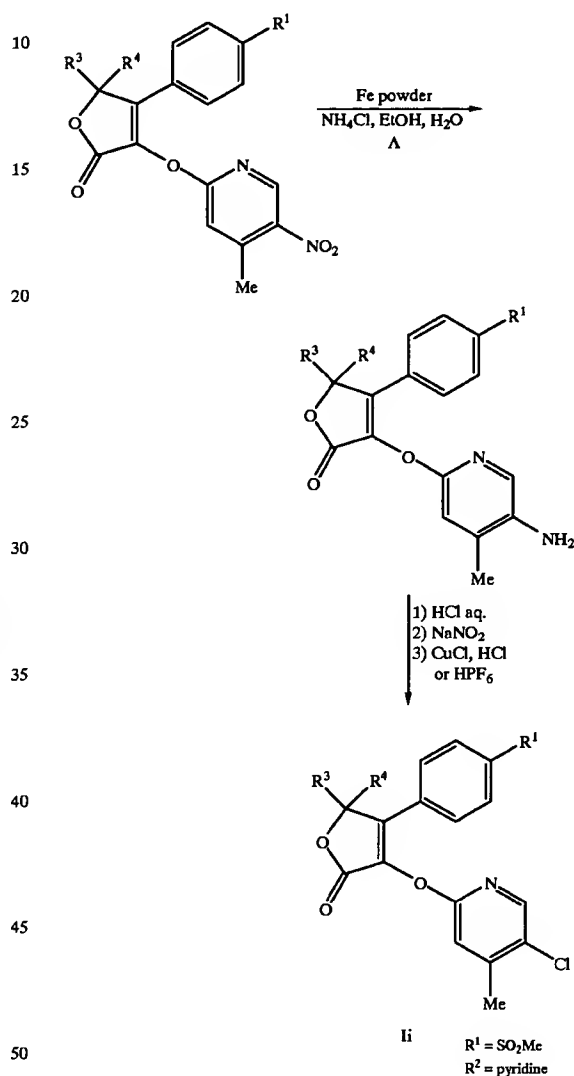


## Method U

An appropriately substituted nitropyridine is reduced with a reagent such as  $\text{Fe}$  (powder) and  $\text{NH}_4\text{Cl}$  in solvents such

46

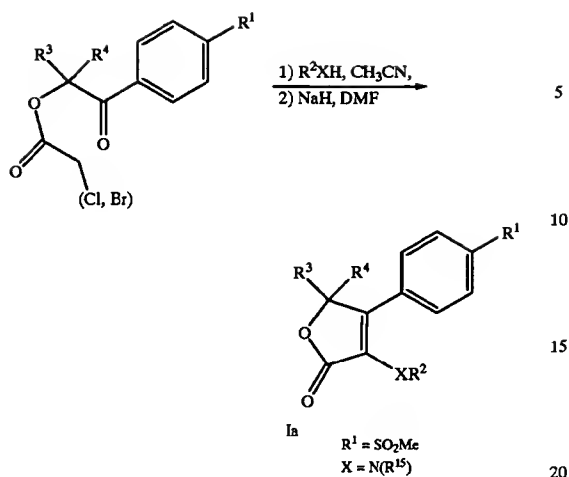
as ethanol and water to give an aminopyridine which is diazotized with  $\text{NaNO}_2$  in aqueous  $\text{HCl}$ , the diazonium salt is decomposed with copper salts such as  $\text{CuCl}$  in  $\text{HCl}$  to give lactone **li**.



## 55 Method W

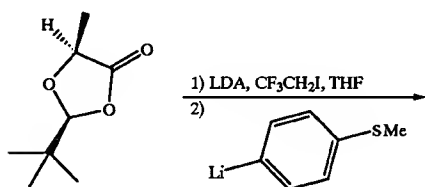
An appropriately substituted halo acetate is reacted with an appropriate secondary amine ( $\text{R}^2(\text{R}^{15})\text{NH}$ ) in a solvent such as  $\text{CH}_3\text{CN}$ ; further treatment with a base such as  $\text{NaH}$  in a solvent such as  $\text{DMF}$  affords lactone **la**.

47



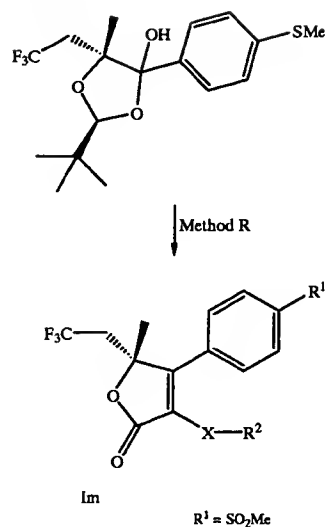
## Method X

An appropriately substituted lactone (*Tetrahedron*, 1984, 40, 1313) is treated with a base such as LDA and reacted with 2,2,2-trifluoroiodoethane. Further treatment with the lithium salt of 4-bromothioanisole gives the desired hemiketal, which is then reacted as in method R to give the desired lactone Im.



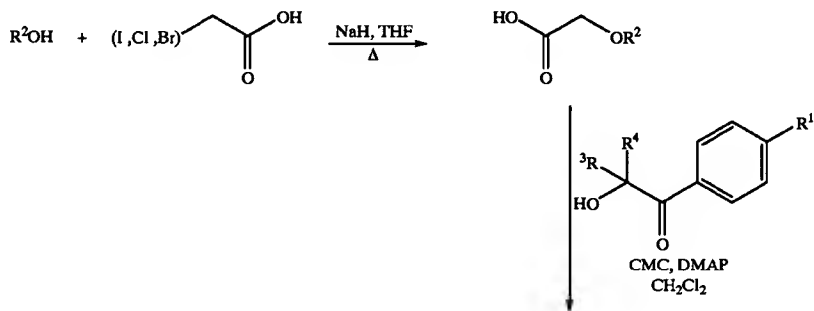
48

-continued

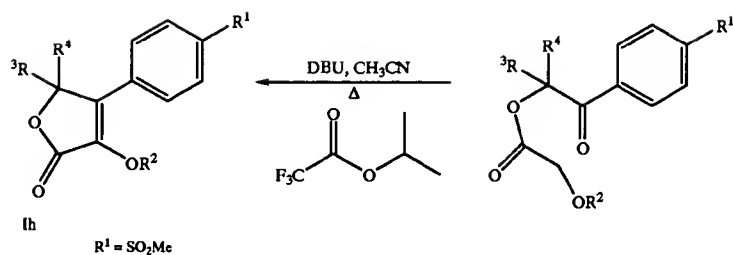


## Method Y

An appropriately substituted alcohol is reacted with an appropriate haloacid such as bromoacetic acid with a base such as NaH in a solvent such as THF to afford an acid ether which is then esterified with an appropriately substituted hydroxyketone with reagents such as CMC and DMAP in a solvent such as  $CH_2Cl_2$  to give a ketoester. The ketoester is then cyclized in the presence of a base such as DBU and a dehydrating reagent such as iso-propyl trifluoroacetate in a solvent such as  $CH_3CN$  to afford lactone Ia.

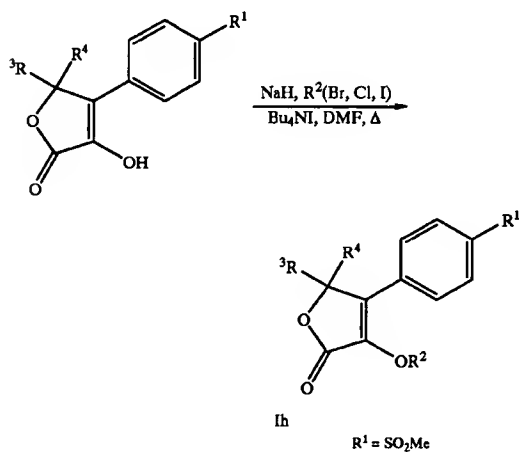


-continued



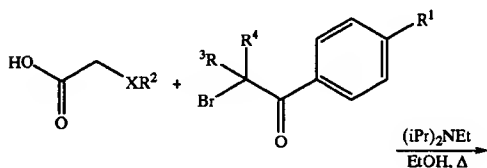
## Method Z

An appropriately substituted hydroxylactone is reacted with an appropriate halide in the presence of a base such as NaH, with a reagent such as  $\text{Bu}_4\text{NI}$  in a solvent such as DMF to afford lactone 1h.

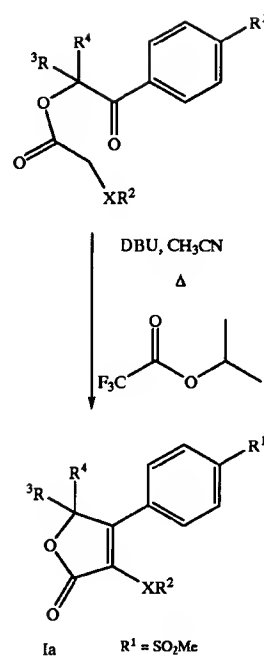


## Method A-1

An appropriately substituted carboxylic acid is esterified with an appropriately substituted haloketone in the presence of a base such as  $(i\text{Pr})_2\text{NEt}$  in a solvent such as EtOH; further treatment with a base such as DBU and a reagent such as iso-propyl 2,2,2-trifluoroacetate in a solvent such as  $\text{CH}_3\text{CN}$  affords lactone 1a.



-continued

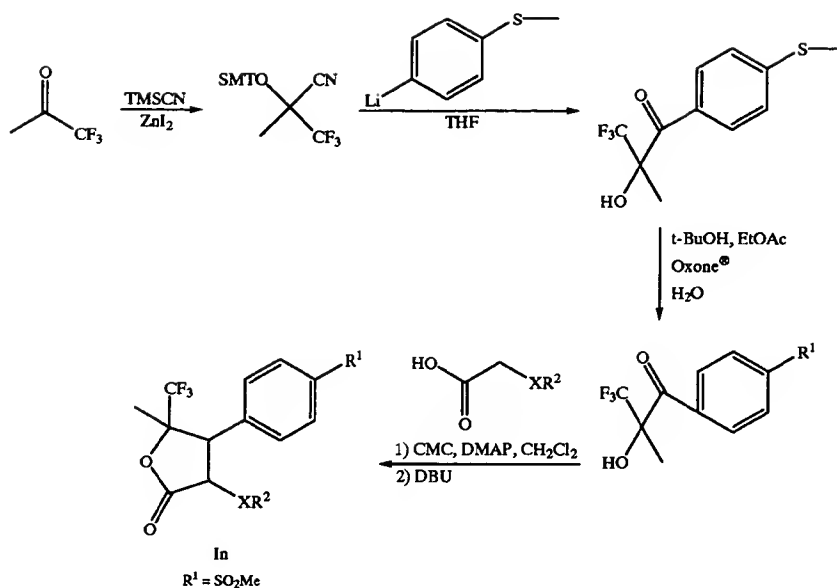


## Method B-1

An appropriately substituted ketone is reacted with a reagent such as TMSCN in the presence of a Lewis acid such as  $\text{ZnI}_2$ , further treatment with a metal salt of thioanisole followed by hydrolysis affords an hydroxyketone. Oxidation of the sulfide with an oxidizing reagent such as Oxone® in solvents such as t-BuOH, EtOAc and water gives the sulfone. Esterification of the alcohol and an appropriately substituted acetic acid with a reagent such as CMC and DMAP in a solvent such as  $\text{CH}_2\text{Cl}_2$  followed by treatment with a base such as DBU gives the lactone 1n.

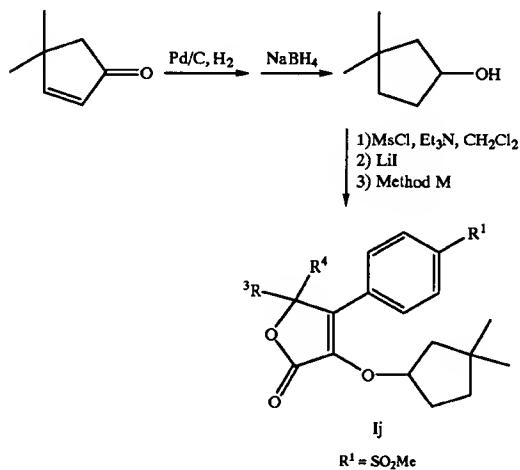
51

52



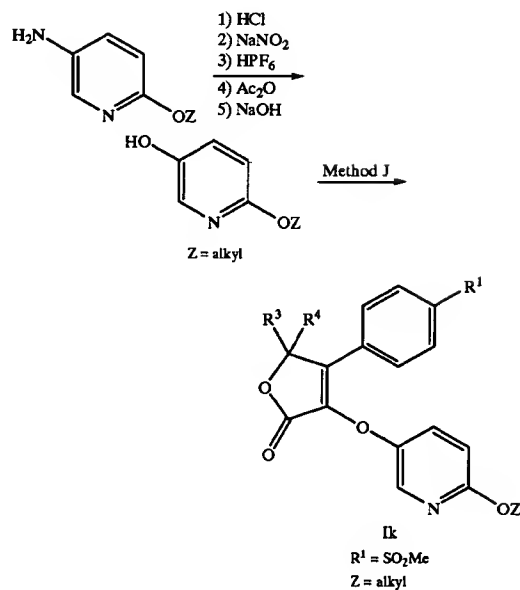
## Method C-1

An appropriately substituted enone is reduced with hydrogen in a solvent such as ethyl acetate with a catalyst such as palladium on activated carbon to give an alcohol. This alcohol was transformed into a leaving group by treatment with reagents such as methanesulfonyl chloride and triethylamine in a solvent such as methylene chloride, followed by treatment in a solvent such as acetone with a reagent such as lithium iodide to afford a compound which was then reacted as in method M to afford lactone Ij.



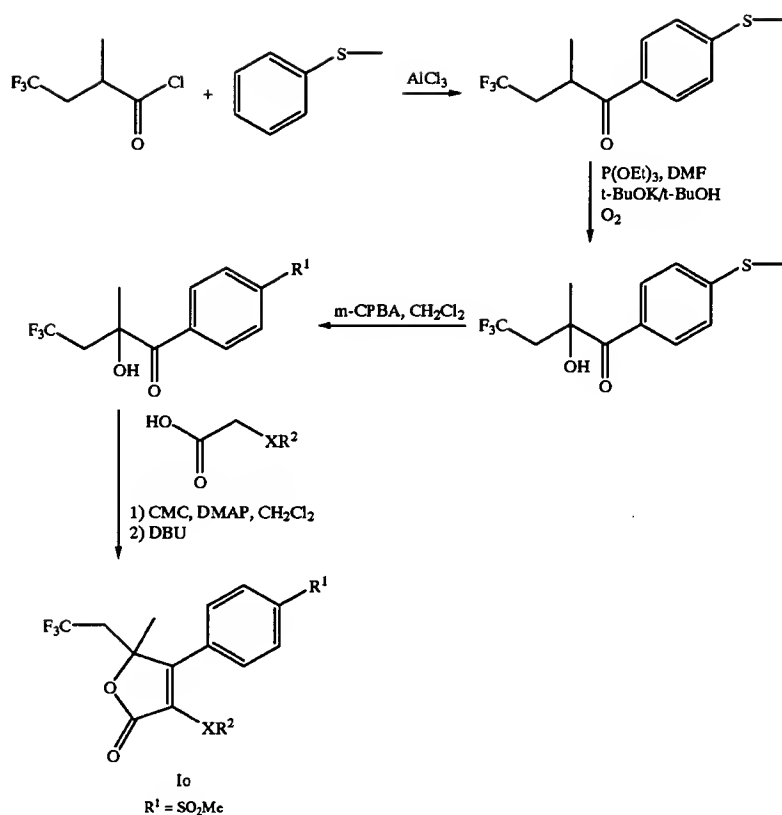
## Method D-1

5-Amino-2-alkoxypyridine is converted to the corresponding diazonium salt and heated with acetic anhydride at 100–110° C. The corresponding 5-acetoxy-2-alkoxypyridine is then hydrolyzed with sodium hydroxide to give the 5-hydroxy-2-alkoxypyridine which is reacted according to method J.



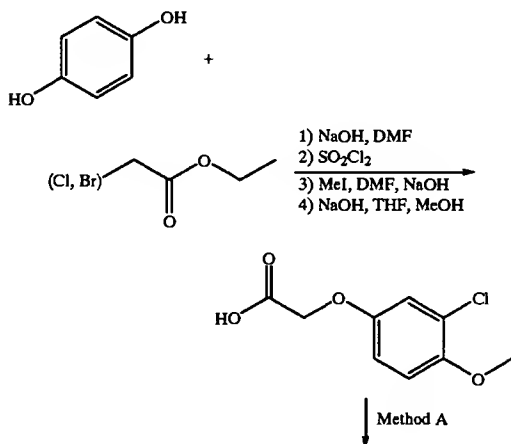
## Method E-1

2(RS)-2-Methyl-4,4,4-trifluorobutyl chloride (GB 2238790-A) is reacted with thioanisole in the presence of a Lewis acid such as AlCl<sub>3</sub>. The ketone is then hydroxylated by air in the presence of potassium t-butoxide and triethyl phosphite, and the sulfide is then oxidized with m-CPBA to the sulfone. The hydroxyketone is then esterified with an appropriately substituted acid in the presence of CMC and DMAP in a solvent such as CH<sub>2</sub>Cl<sub>2</sub> to give an intermediate ester which is cyclized with a base such as DBU to give lactone Io.

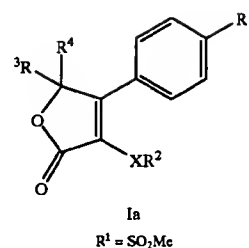


## Method F-1

Hydroquinone is reacted with a halosubstituted acetate, chlorinated with sulfur chloride, methylated with iodomethane in the presence of a base and followed by hydrolysis with sodium hydroxide to give the substituted phenoxy acetic acid, which is reacted according to method A to afford lactone Ia.

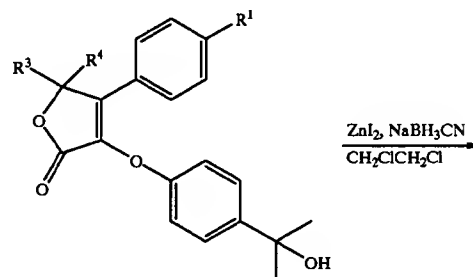


-continued



## Method G-1

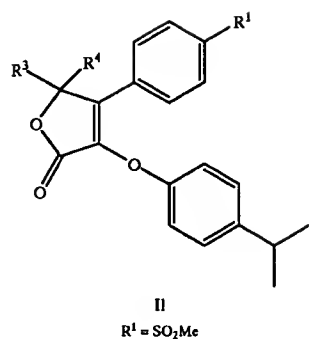
An appropriately substituted 3-(4-(1-hydroxy-1-methyl)ethylphenoxy)-5H-furan-2-one is reduced with NaBH<sub>3</sub>CN in the presence of ZnI<sub>2</sub> to give lactone II.





55

-continued

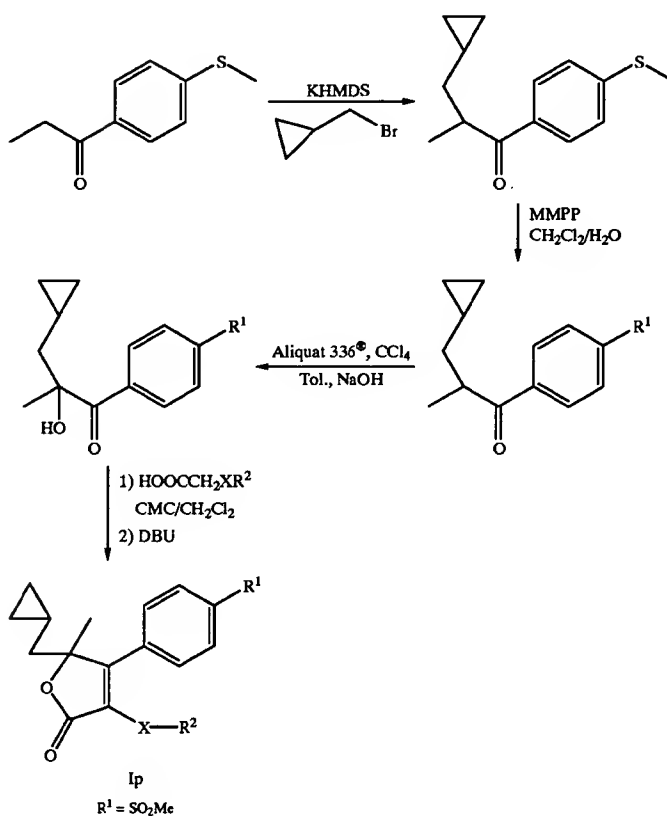


15

56

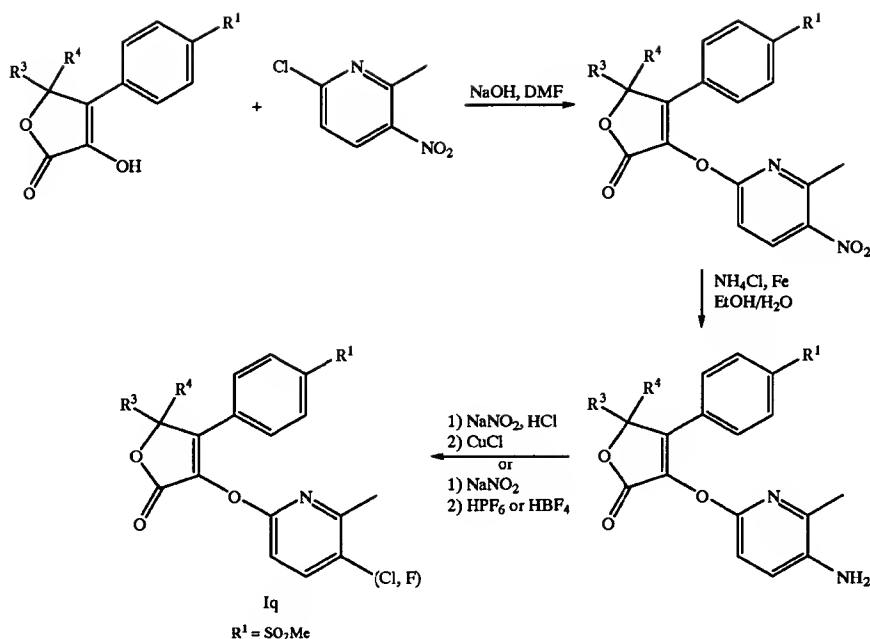
## Method H-1

5 An appropriately substituted alkyl (4-thiomethyl)phenyl ketone is alkylated with bromomethylcyclopropane using a base such as KHMDS. The methyl sulfide is oxidized with MMPP to the corresponding sulfone and hydroxylated by NaOH and CCl<sub>4</sub> in toluene in the presence of a phase transfer catalyst such as Aliquat 336®. The hydroxyketone is then esterified with an appropriately substituted acid in the presence of CMC and DMAP in a solvent such as CH<sub>2</sub>Cl<sub>2</sub> to give an intermediate ester which is cyclized with a base such as DBU to give lactone Ip.



## Method I-1

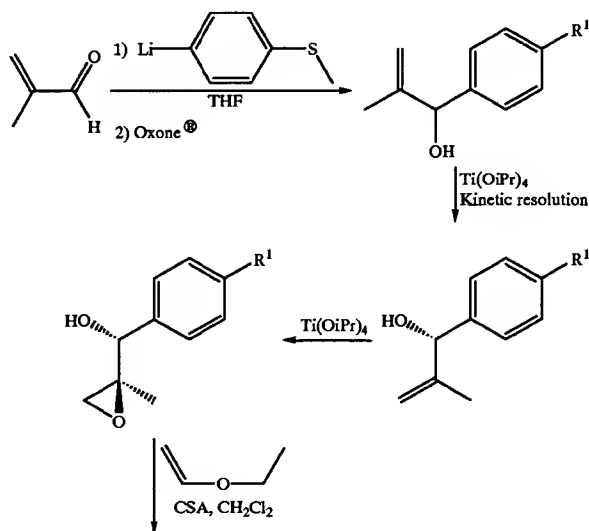
55 An appropriately substituted hydroxylactone is reacted with an appropriately substituted nitropyridine in the presence of a base such as NaOH in DMF at 100–110° C. The nitro group of the coupling product is then reduced with Fe (powder) and NH<sub>4</sub>Cl in solvents such as ethanol and water. The amino group is diazotized and the resulting diazonium salt is decomposed in the presence of appropriate copper salt such as CuCl or CuBr to give lactone 1q. Alternatively, the diazonium salt is treated HBF<sub>4</sub> or HPF<sub>6</sub> to give after heating the fluoro-substituted lactone pyridine 1q.

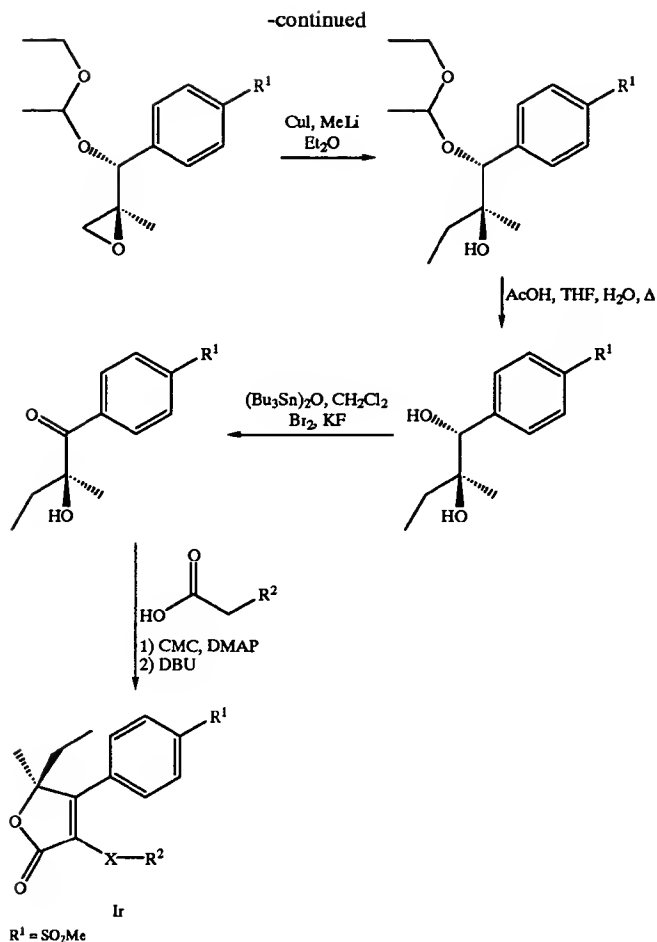


#### Method J-1

The lithium reagent prepared from 4-bromothioanisole and *n*-BuLi at  $-72^\circ\text{C}$ . is reacted with methacrolein and the resulting product is oxidized with an oxidizing reagent such as Oxone® to the methyl sulfone. A kinetic resolution by Sharpless epoxidation reaction using (+)-diisopropyl tartrate and *t*-butyl hydroperoxide provides the (S)-allylic alcohol, which is epoxidized by (–)-diisopropyl tartrate and *t*-butyl hydroperoxide. The alcohol of the epoxy alcohol is protected

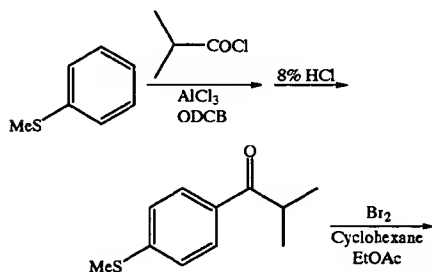
as an ethoxyethyl ether and the epoxide is reacted with dimethyl cuprate (from methyllithium and copper(I) iodide). The ethoxyethyl ether is then cleaved and the resulting diol is treated with  $(\text{Bu}_3\text{Sn})_2\text{O}$  and oxidized with  $\text{Br}_2$  to give the (S)-alcohol. The hydroxyketone is then esterified with an appropriately substituted acid in the presence of CMC and DMAP in a solvent such as  $\text{CH}_2\text{Cl}_2$  to give an intermediate ester which is cyclized with a base such as DBU to give lactone Ir.



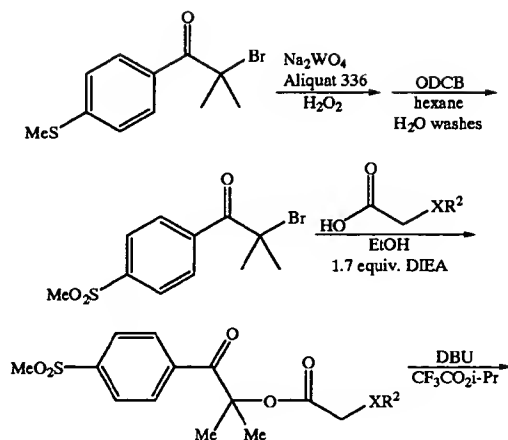


## Method K-1

4-Bromothiobanisole is reacted with isobutyryl chloride in the presence of aluminum chloride in *o*-dichlorobenzene (ODCB). The resulting ketone is brominated and oxidized with  $\text{Na}_2\text{WO}_4$  and  $\text{H}_2\text{O}_2$  in the presence of Aliquat 336 to the bromoketone methyl sulfone. The bromoketone is then reacted with an appropriate alkoxy or aryloxy acetic acid in the presence DIEA and the ester intermediate is cyclized and dehydrated with DBU in the presence of isopropyl trifluoroacetate to give lactone Ia.

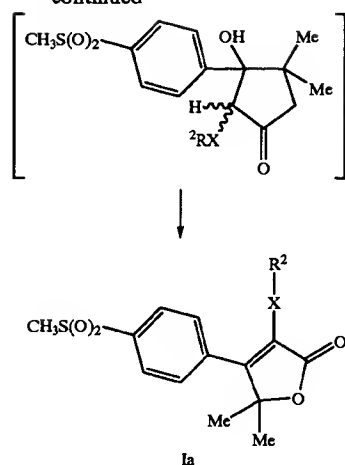


-continued



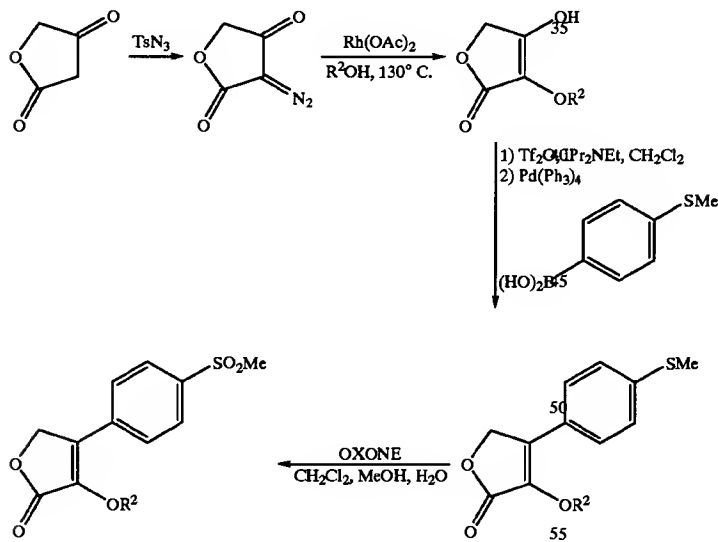
61

-continued



## Method L-1

Tetronic acid is converted to the  $\alpha$ -diazoketone derivative with tosyl azide (see Stachel et al., *Liebigs Ann. Chem.* 1994, P.129 for a similar preparation). The diazo compound is reacted with an appropriately substituted alcohol in the presence of rhodium acetate (see Stachel et al., *Liebigs Ann. Chem.* 1994 P. 129) to give an ether. This compound is treated with triflic anhydride followed by a Suzuki type coupling reaction with 4-methylthiophenyl boronic acid (Wong et al., *Tetrahedron Lett.* 1993, p. 8237.) The sulfide is then oxidized with OXONE® to provide 1s.



62

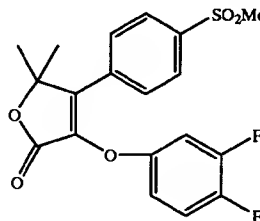
## Representative Compounds

Tables I illustrates novel compounds of the present invention.

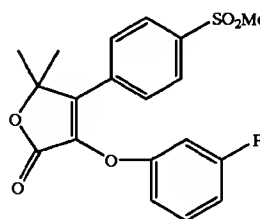
TABLE I

Example	Method
---------	--------

1 A



2 A

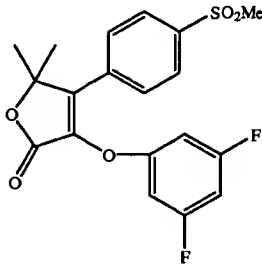
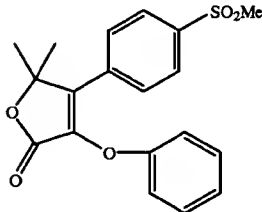
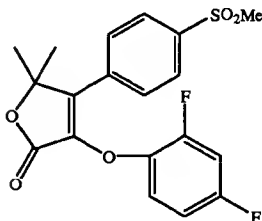
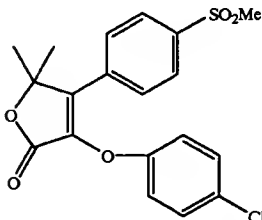
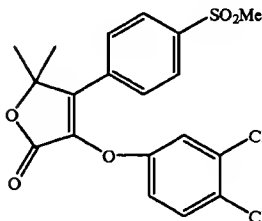
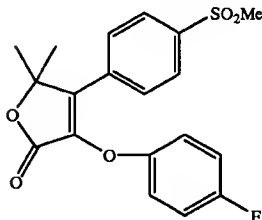


60

65

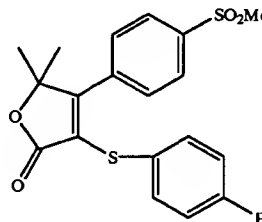
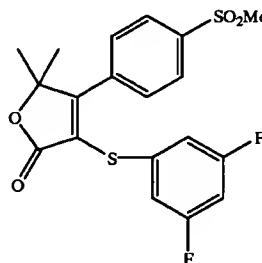
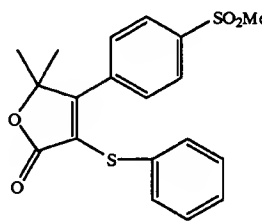
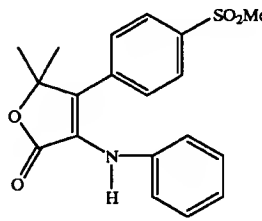
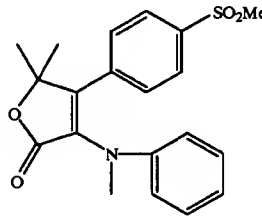
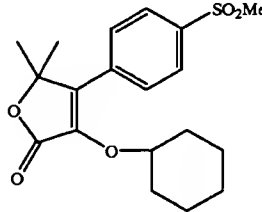
63

TABLE I-continued

	Example	Method
	3	A
	4	F
	5	B
	6	A
	7	A
	8	A

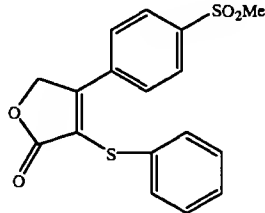
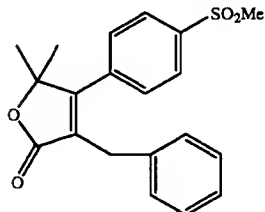
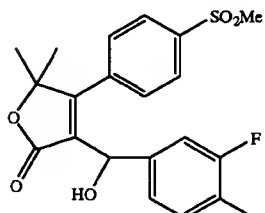
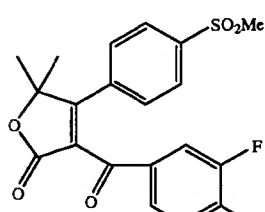
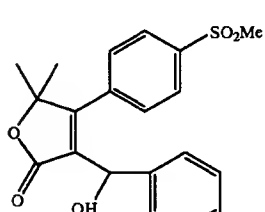
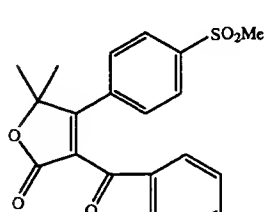
64

TABLE I-continued

	Example	Method
	9	A
	10	C
	11	A
	12	D
	13	D
	14	E

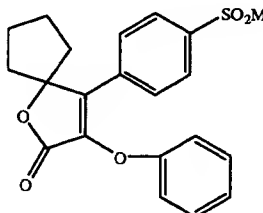
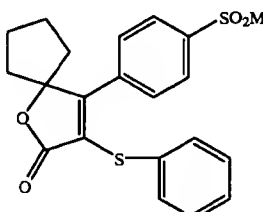
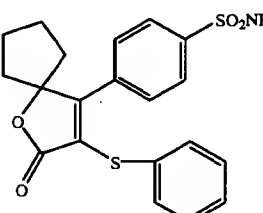
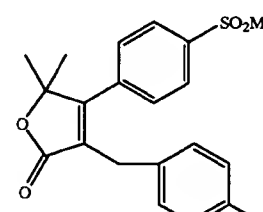
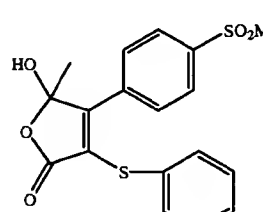
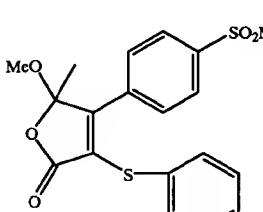
65

TABLE I-continued

	Example	Method
	15	E
	16	F
	17	G
	18	G
	19a	G
	19b	G

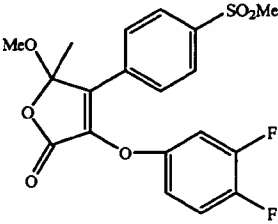
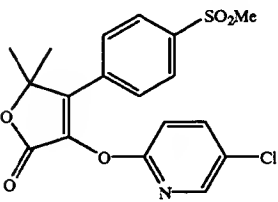
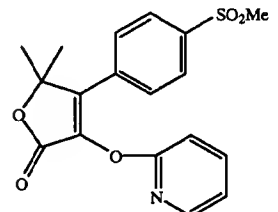
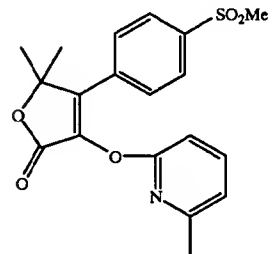
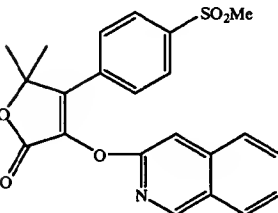
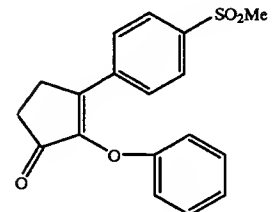
66

TABLE I-continued

	Example	Method
	20	A
	21	A
	22	H
	23	F
	24a	I
	24b	I

67

TABLE I-continued

	Example	Method
	24c	I
	25	J
	26	J
	27	J
	28	J
	29	K

68

TABLE I-continued

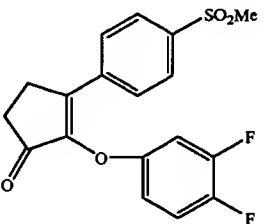
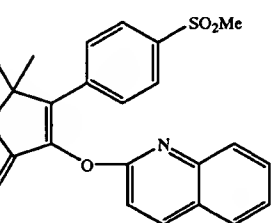
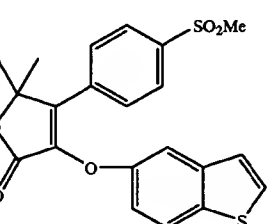
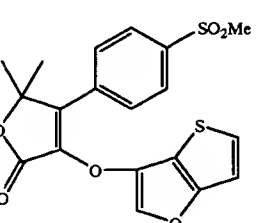
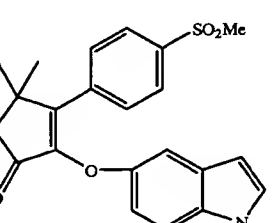
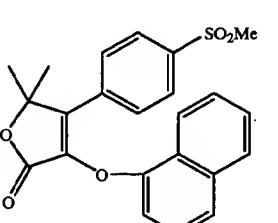
	Example	Method
	30	Q
	31	J
	32	J
	33	
	34	
	35	

TABLE I-continued

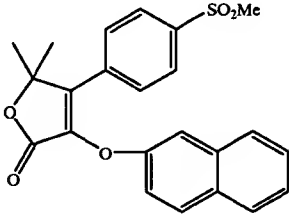
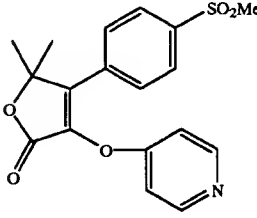
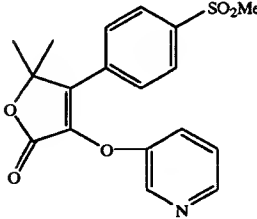
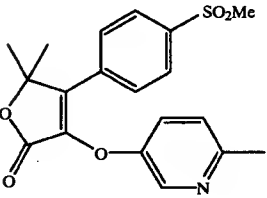
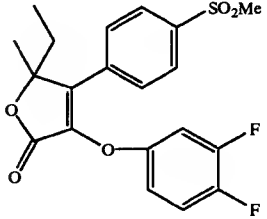
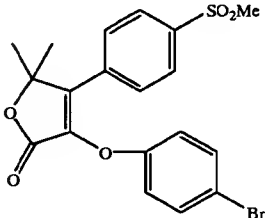
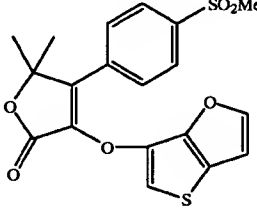
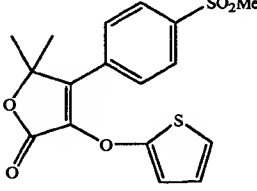
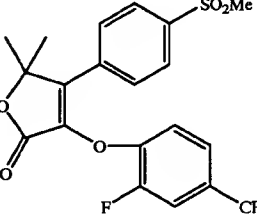
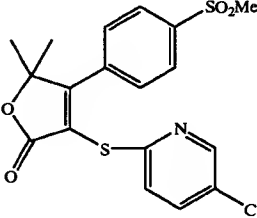
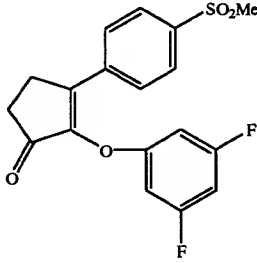
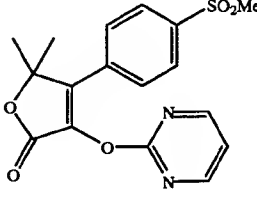
	Example	Method
	36	
	37	J
	38	J
	39	J
	40	
	41	

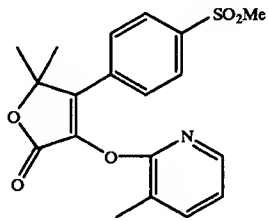
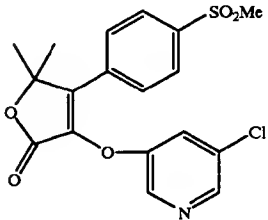
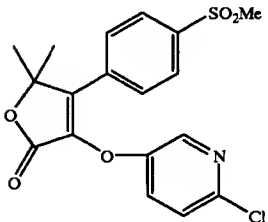
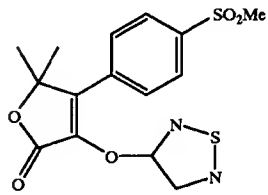
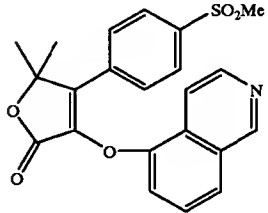
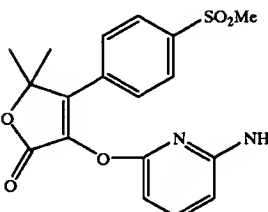
TABLE I-continued

	Example	Method
	42	
	43	
	44	J
	45	J
	46	K
	47	J



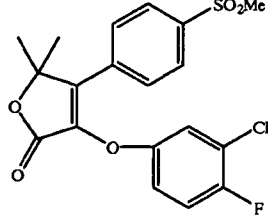
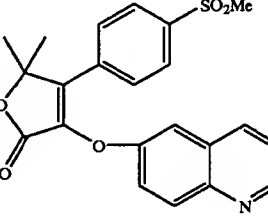
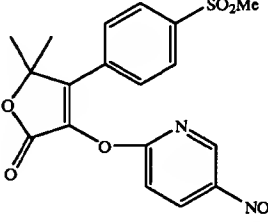
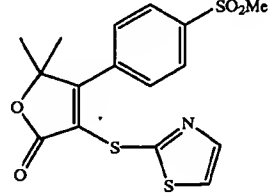
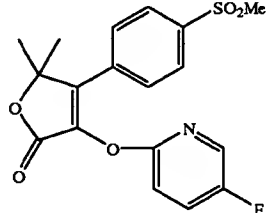
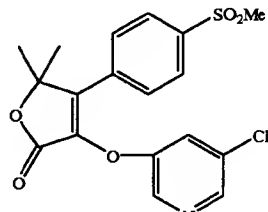
71

TABLE I-continued

	Example	Method
	48	S
	49	J
	50	J
	51	J
	52	J
	53	J

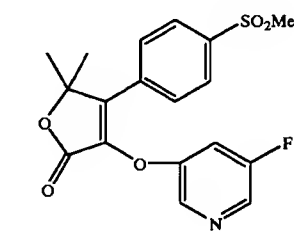
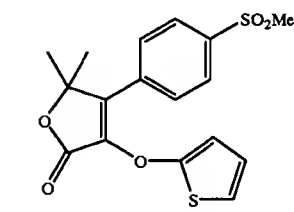
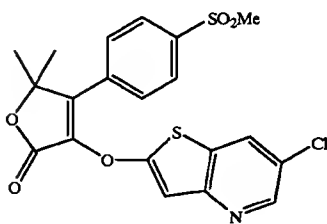
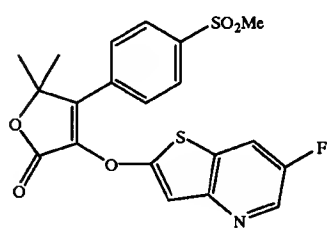
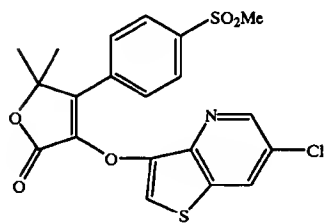
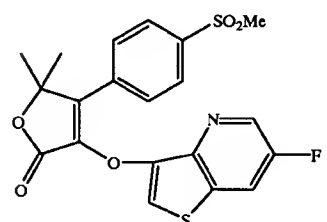
72

TABLE I-continued

	Example	Method
	54	J
	55	J
	56	J
	57	J
	58	J
	59	

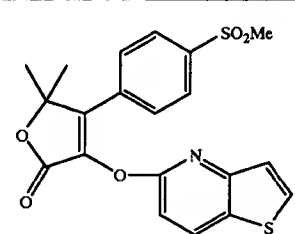
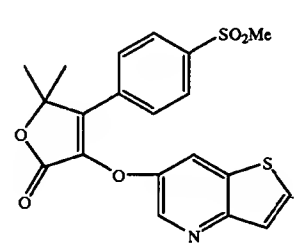
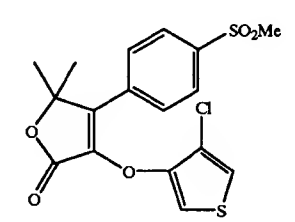
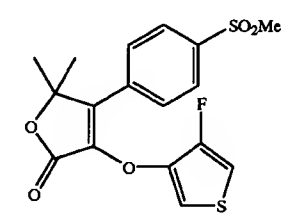
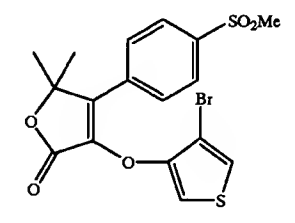
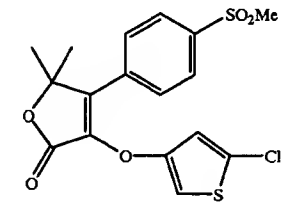
73

TABLE I-continued

	Example	Method
	60	
	61	
	62	
	63	
	64	
	65	

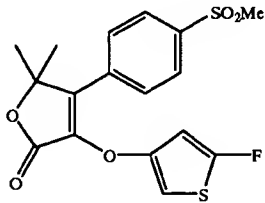
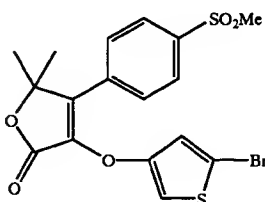
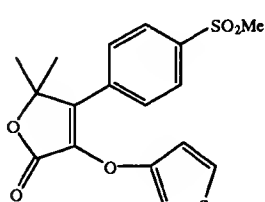
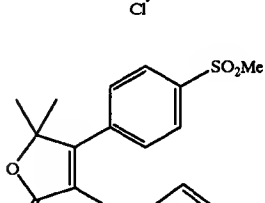
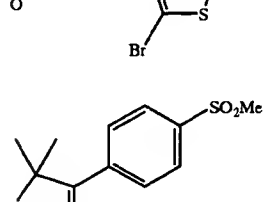
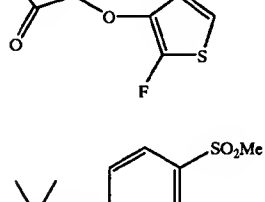
74

TABLE I-continued

	Example	Method
	66	
	67	
	68	
	69	
	70	
	71	

75

TABLE I-continued

Example	Method
72	5
	
73	10
	
74	15
	
75	20
	
76	25
	
77	30
	

76

TABLE I-continued

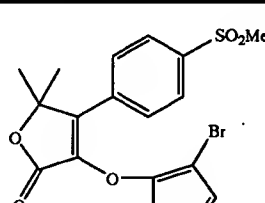
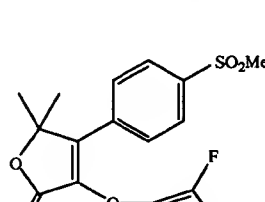
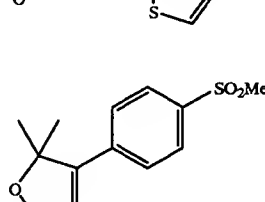
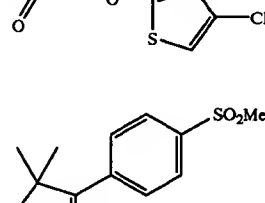
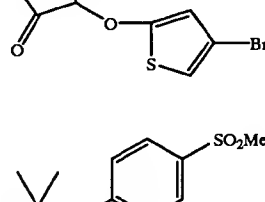
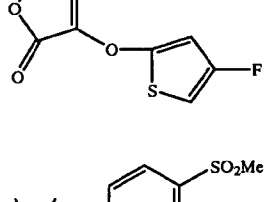
Example	Method
78	5
	
79	10
	
80	15
	
81	20
	
82	25
	
83	30
	

TABLE I-continued

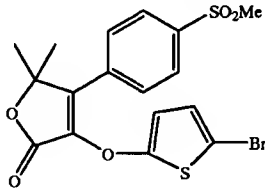
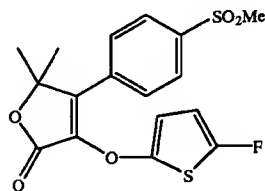
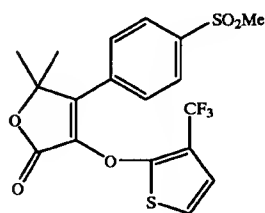
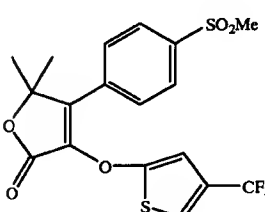
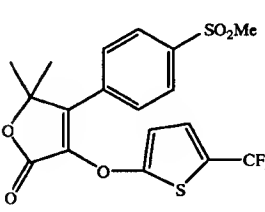
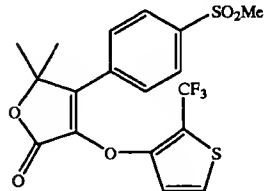
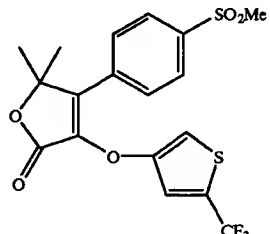
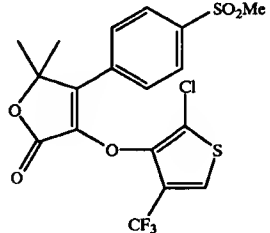
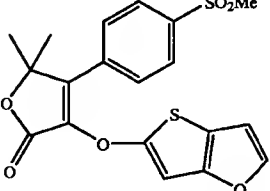
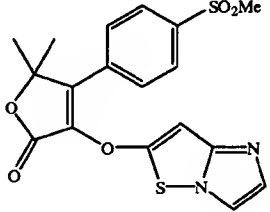
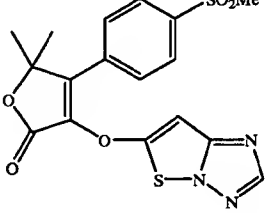
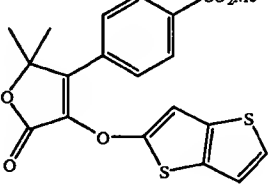
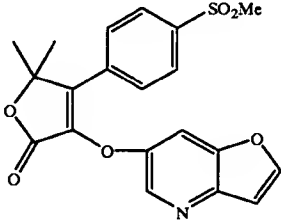
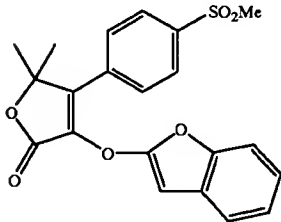
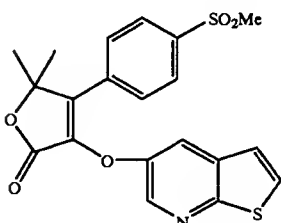
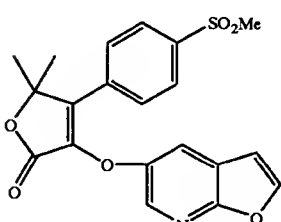
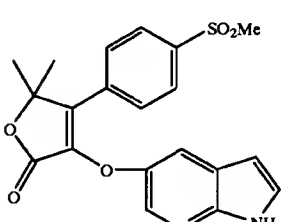
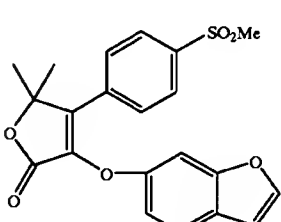
	Example	Method
	84	
	85	
	86	
	87	
	88	
	89	

TABLE I-continued

	Example	Method
	90	
	91	
	92	
	93	
	94	
	95	

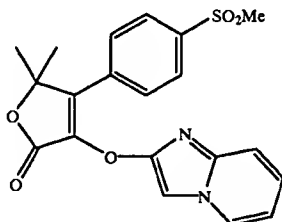
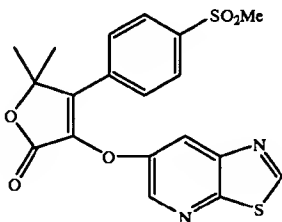
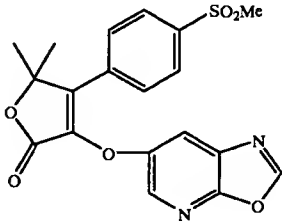
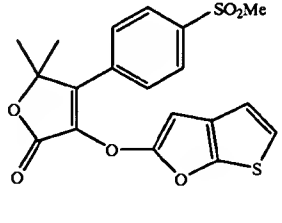
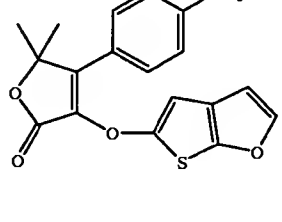
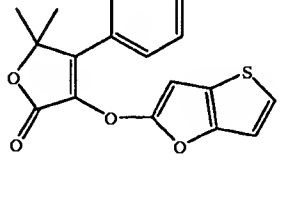
79

TABLE I-continued

	Example	Method
	96	
	97	
	98	
	99	
	100	
	101	

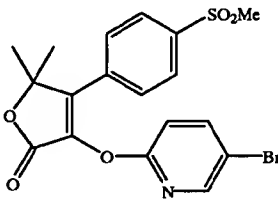
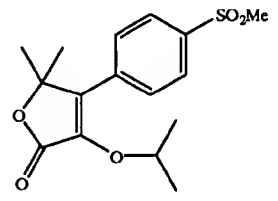
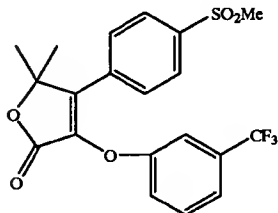
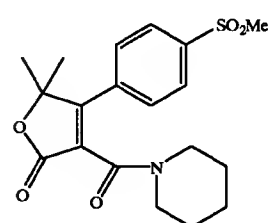
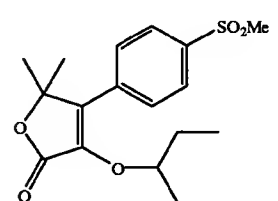
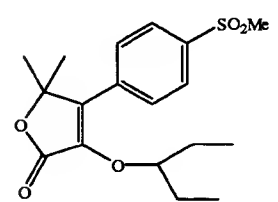
80

TABLE I-continued

	Example	Method
	102	
	103	
	104	
	105	
	106	
	107	

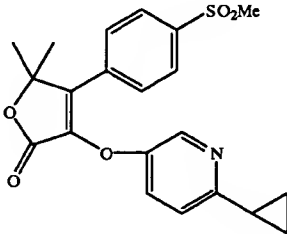
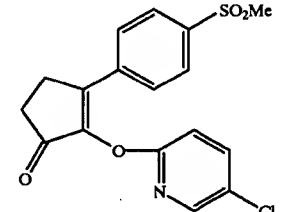
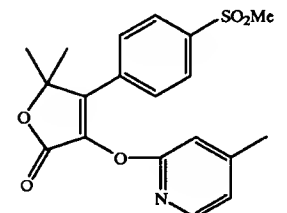
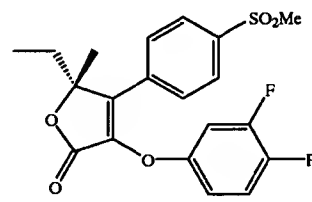
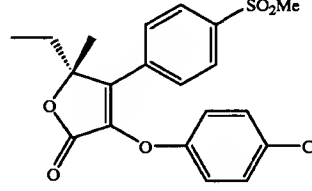
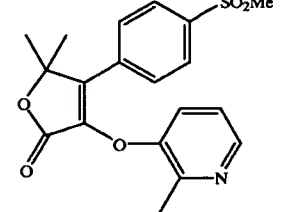
81

TABLE I-continued

	Example	Method
	108	L
	109	M or K-1
	110	J
	111	N
	112	M
	113	O

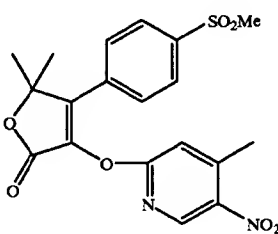
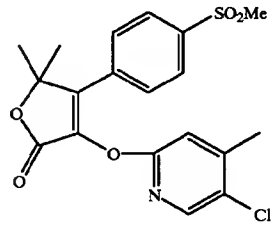
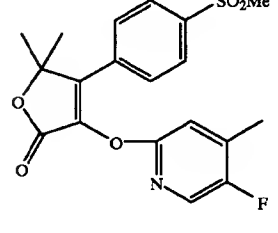
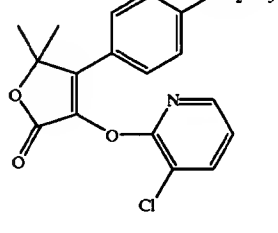
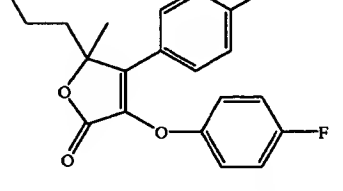
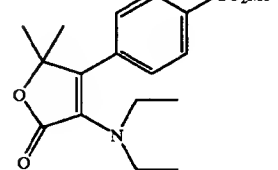
82

TABLE I-continued

	Example	Method
	114	
	115	K
	116	J
	117	R
	118	R
	119	J

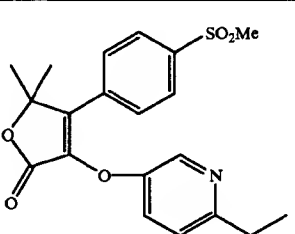
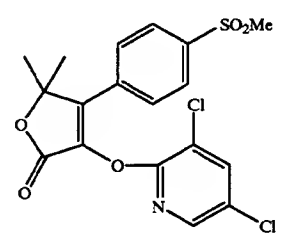
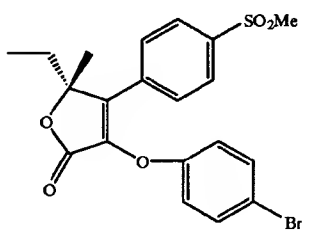
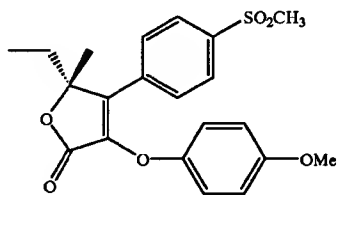
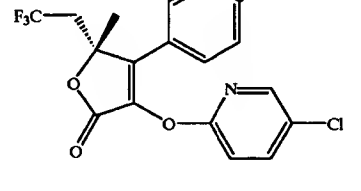
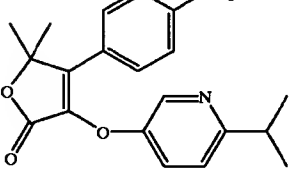
83

TABLE I-continued

	Example	Method
	120	T
	121	U
	122	U
	123	T + U
	124	J
	125	W

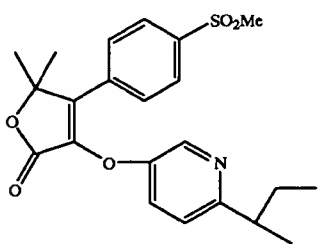
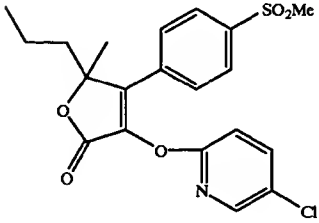
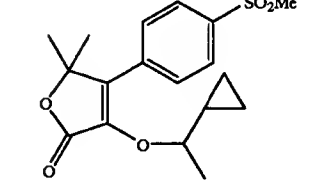
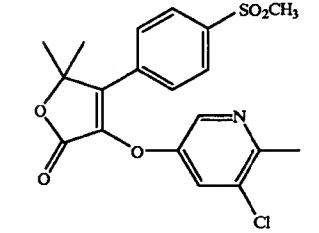
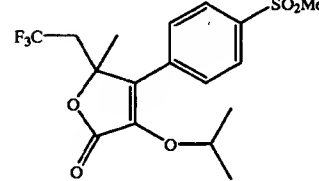
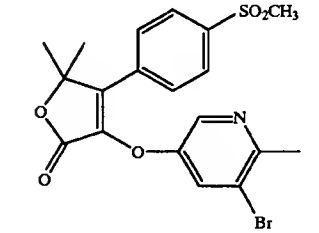
84

TABLE I-continued

	Example	Method
	126	
	127	J
	128	R
	129	J
	130	X + R
	131	

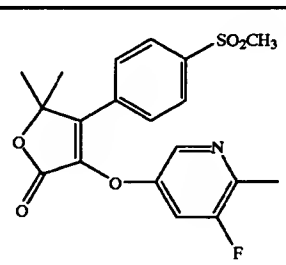
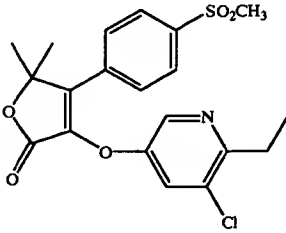
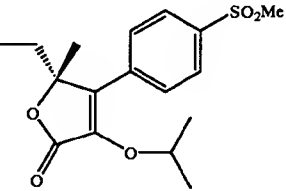
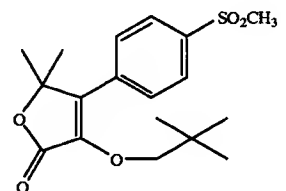
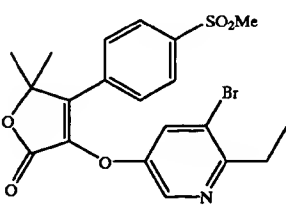
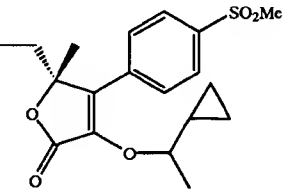
85

TABLE I-continued

	Example	Method
	132	
	133	J
	134	Y
	135	
	136	M
	137	

86

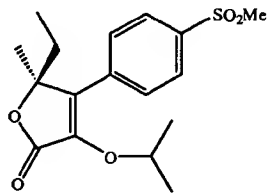
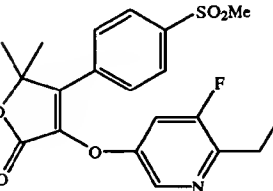
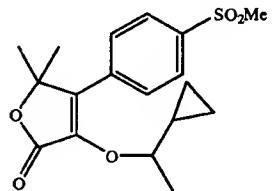
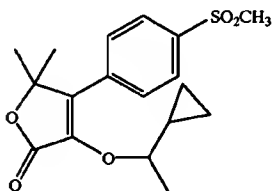
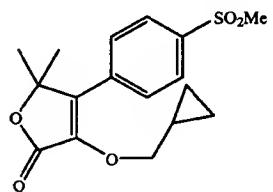
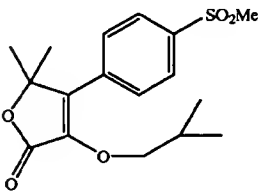
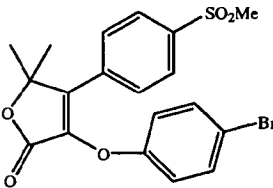
TABLE I-continued

	Example	Method
	138	
	139	
	140	M
	141	Z
	142	
	143	Y



87

TABLE I-continued

	Example	Method
	144	J-1
	145	
	146	Y
	147	Y
	148	Z
	149	Z
	150	A

88

TABLE I-continued

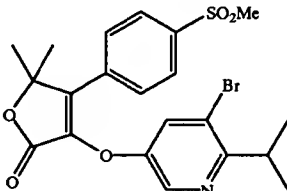
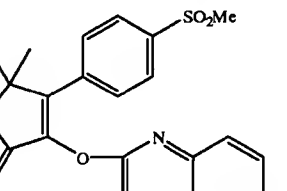
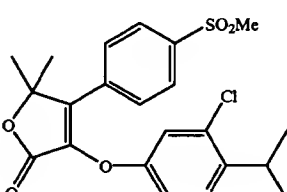
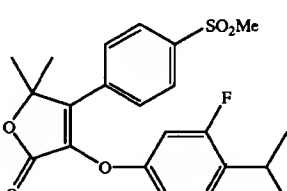
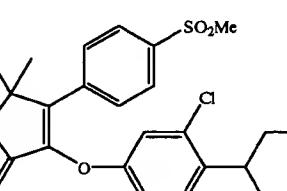
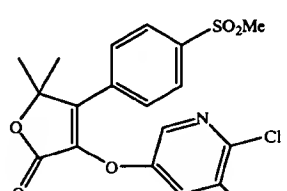
	Example	Method
	151	
	152	
	153	
	154	
	155	
	156	

TABLE I-continued

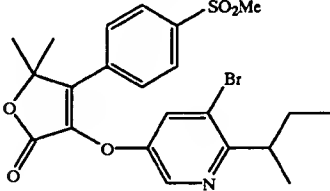
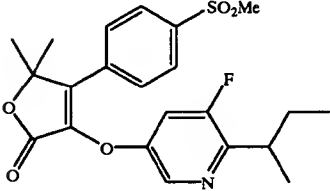
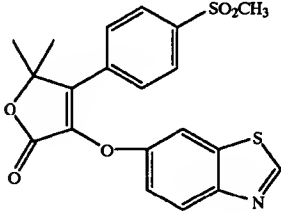
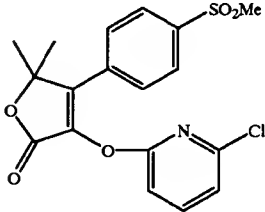
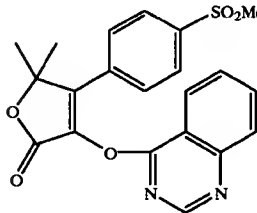
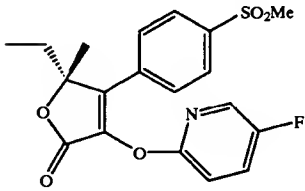
	Example	Method
	157	
	158	
	159	J
	160	J
	161	J
	162	J

TABLE I-continued

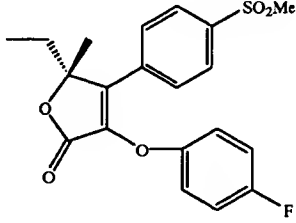
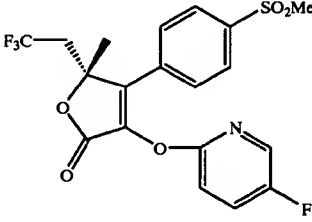
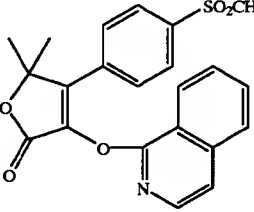
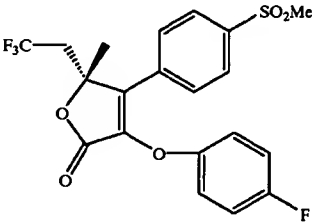
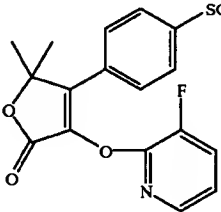
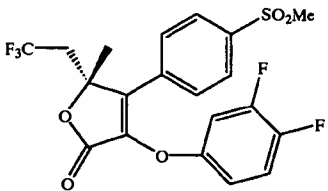
	Example	Method
	163	A
	164	J
	165	J
	166	A
	167	B
	168	X + J

TABLE I-continued

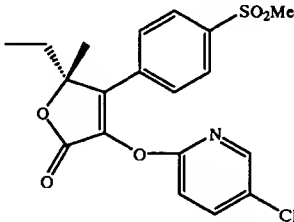
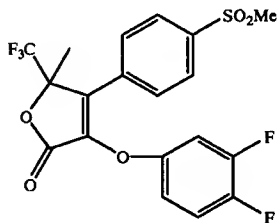
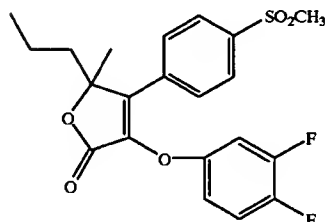
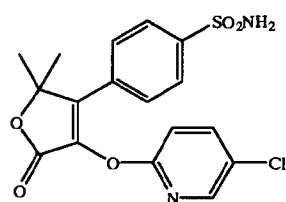
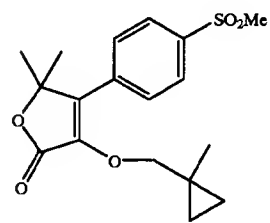
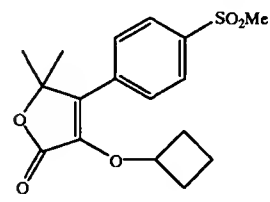
	Example	Method
	169	A
	170	B-1
	171	A
	172	
	173	
	174	E

TABLE I-continued

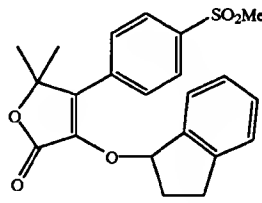
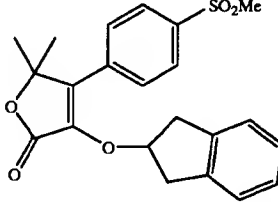
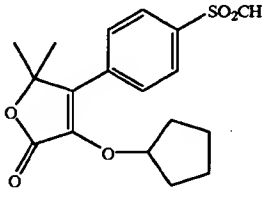
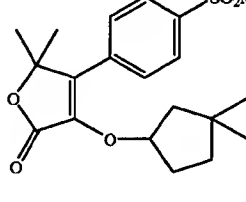
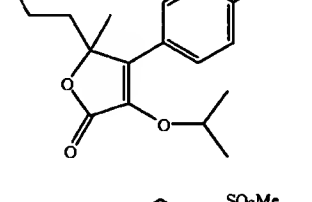
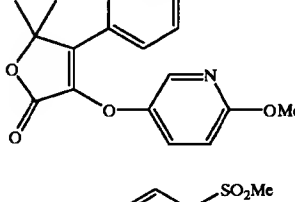
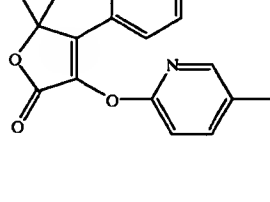
	Example	Method
	175	E
	176	E
	177	M
	178	C-1
	179	A
	180	D-1
	181	J

TABLE I-continued

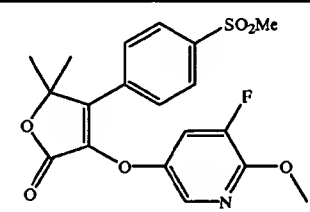
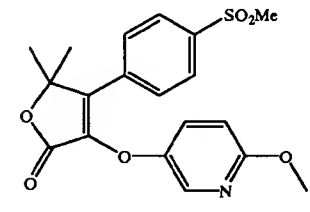
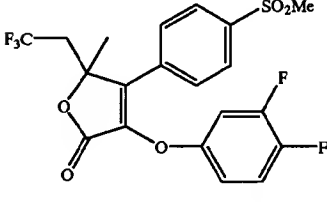
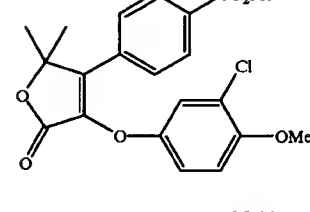
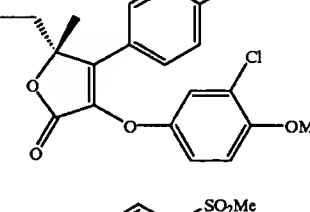
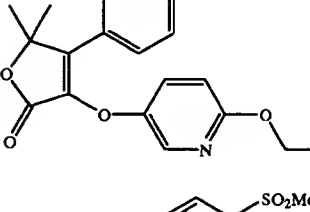
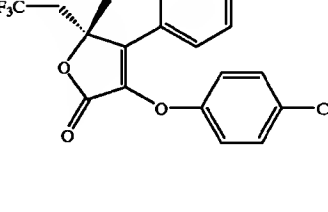
	Example	Method
	182	
	183	
	184	E-1
	185	F-1 + A
	186	F-1 + A
	187	
	188	R

TABLE I-continued

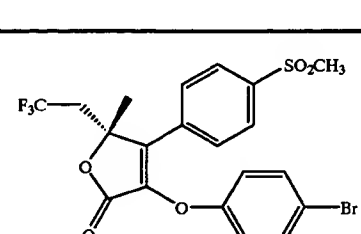
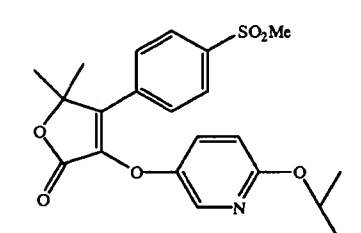
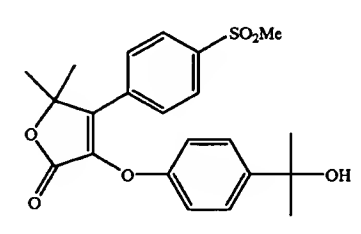
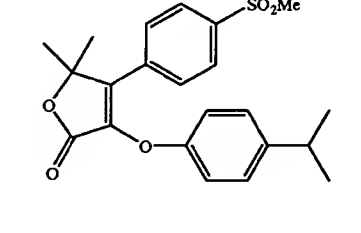
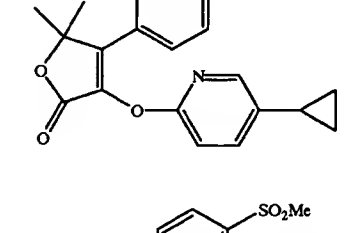
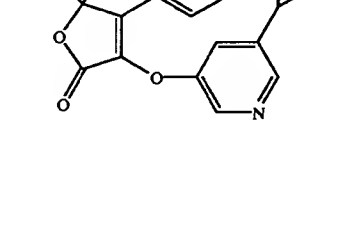
	Example	Method
	189	R
	190	
	191	
	192	
	193	
	194	

TABLE I-continued

	Example	Method
	195	H-1
	196	J
	197	J
	198	J
	199	J
	200	L
	201	J

TABLE I-continued

	Example	Method
	202	L
	203	I-1
	204	
	205	
	206	
	207	L-1
	208	L-1

## Assays for determining Biological Activity

The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

## INHIBITION OF CYCLOOXYGENASE ACTIVITY

Compounds are tested as inhibitors of cyclooxygenase activity in whole cell cyclooxygenase assays. Both of these assays measure prostaglandin  $E_2$  synthesis in response to arachidonic acid, using a radioimmunoassay. Cells used for these assays are human osteosarcoma 143 cells (which specifically express COX-2) and human U-937 cells (which specifically express COX-1). In these assays, 100% activity is defined as the difference between prostaglandin  $E_2$  synthesis in the absence and presence of arachidonate.

## Whole Cell Assays

For cyclooxygenase assays, osteosarcoma cells are cultured in 1 mL of media in 24-well multidishes (Nunc) until confluent ( $1-2 \times 10^5$  cells/well). U-937 cells are grown in spinner flasks and resuspended to a final density of  $1.5 \times 10^6$  cells/mL in 24-well multidishes (Nunc). Following washing and resuspension of osteosarcoma and U-937 cells in 1 mL of HBSS, 1  $\mu$ L of a DMSO solution of test compound or DMSO vehicle is added, and samples gently mixed. All assays are performed in triplicate. Samples are then incubated for 5 or 15 minutes at 37° C., prior to the addition of arachidonic acid. Arachidonic acid (peroxide-free, Cayman Chemical) is prepared as a 10 mM stock solution in ethanol and further diluted 10-fold in HBSS. An aliquot of 10  $\mu$ L of this diluted solution is added to the cells to give a final arachidonic acid concentration of 10  $\mu$ M. Control samples are incubated with ethanol vehicle instead of arachidonic acid. Samples are again gently mixed and incubated for a further 10 min. at 37° C. For osteosarcoma cells, reactions are then stopped by the addition of 100  $\mu$ L of 1N HCl, with mixing and by the rapid removal of the solution from cell monolayers. For U-937 cells, reactions are stopped by the addition of 100  $\mu$ L of 1N HCl, with mixing. Samples are then neutralized by the addition of 100  $\mu$ L of 1N NaOH and PGE<sub>2</sub> levels measured by radioimmunoassay. Whole cell assays for COX-2 and COX-1 using CHO transfected cell lines

Chinese hamster ovary (CHO) cell lines which have been stably transfected with an eukaryotic expression vector pCDNAIII containing either the human COX-1 or COX-2 cDNA's are used for the assay. These cell lines are referred to as CHO [hCOX-1] and CHO [hCOX-2], respectively. For cyclooxygenase assays, CHO[hCOX-1] cells from suspension cultures and CHO[hCOX-2] cells prepared by trypsinization of adherent cultures are harvested by centrifugation (300 $\times$ g, 10 min) and washed once in HBSS containing 15 mM HEPES, pH 7.4, and resuspended in HBSS, 15 mM HEPES, pH 7.4, at a cell concentration of  $1.5 \times 10^6$  cells/mL. Drugs to be tested are dissolved in DMSO to 66.7-fold the highest test drug concentration. Compounds are typically tested at 8 concentrations in duplicate using serial 3-fold serial dilutions in DMSO of the highest drug concentration. Cells ( $0.3 \times 10^6$  cells in 200  $\mu$ L) are preincubated with 3  $\mu$ L of the test drug or DMSO vehicle for 15 min at 37° C. Working solutions of peroxide-free AA (5.5  $\mu$ M and 110  $\mu$ M AA for the CHO [hCOX-1] and CHO [COX-2] assays, respectively) are prepared by a 10-fold dilution of a concentrated AA solution in ethanol into HBSS containing 15 mM HEPES, pH 7.4. Cells are then challenged in the presence or absence of drug with the AA/HBSS solution to yield a final concentration of 0.5  $\mu$ M AA in the CHO[hCOX-

1] assay and a final concentration of 10  $\mu$ M AA in the CHO[hCOX-2] assay. The reaction is terminated by the addition of 10  $\mu$ L 1 N HCl followed by neutralization with 20  $\mu$ L of 0.5 N NaOH. The samples are centrifuged at 300 $\times$ g at 4° C. for 10 min, and an aliquot of the clarified supernatant is appropriately diluted for the determination of PGE<sub>2</sub> levels using an enzyme-linked immunoassay for PGE<sub>2</sub> (Correlate PGE<sub>2</sub> enzyme immunoassay kit, Assay Designs, Inc.). Cyclooxygenase activity in the absence of test compounds is determined as the difference in PGE<sub>2</sub> levels of cells challenged with arachidonic acid versus the PGE<sub>2</sub> levels in cells mock-challenged with ethanol vehicle. Inhibition of PGE<sub>2</sub> synthesis by test compounds is calculated as a percentage of the activity in the presence of drug versus the activity in the positive control samples.

## Assay of COX-1 Activity from U937 cell microsomes

U 937 cells are pelleted by centrifugation at 500 $\times$ g for 5 min and washed once with phosphate-buffered saline and repelleted. Cells are resuspended in homogenization buffer consisting of 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, 2  $\mu$ g/ml leupeptin, 2  $\mu$ g/ml soybean trypsin inhibitor, 2  $\mu$ g/ml aprotinin and 1 mM phenyl methyl sulfonyl fluoride. The cell suspension is sonicated 4 times for 10 sec and is centrifuged at 10,000 $\times$ g for 10 min at 4° C. The supernatant is centrifuged at 100,000 $\times$ g for 1 hr at 4° C. The 100,000 $\times$ g microsomal pellet is resuspended in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA to approximately 7 mg protein/mL and stored at -80° C.

Microsomal preparations are thawed immediately prior to use, subjected to a brief sonication, and then diluted to a protein concentration of 125  $\mu$ g/mL in 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA, 0.5 mM phenol, 1 mM reduced glutathione and 1  $\mu$ M hematin. Assays are performed in duplicate in a final volume of 250  $\mu$ L. Initially, 5  $\mu$ L of DMSO vehicle or drug in DMSO are added to 20  $\mu$ L of 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA in wells of a 96-deepwell polypropylene titre plate. 200  $\mu$ L of the microsomal preparation are then added and preincubated for 15 min at room temperature before addition of 25  $\mu$ L of 1 M arachidonic acid in 0.1 M Tris-HCl and 10 mM EDTA, pH 7.4. Samples are incubated for 40 min at room temperature and the reaction is stopped by the addition of 25  $\mu$ L of 1 N HCl. Samples are neutralized with 25  $\mu$ L of 1 N NaOH prior to quantitation of PGE<sub>2</sub> content by radioimmunoassay (Dupont-NEN or Amersham assay kits). Cyclooxygenase activity is defined as the difference between PGE<sub>2</sub> levels in samples incubated in the presence of arachidonic acid and ethanol vehicle.

## Assay of the activity of purified human COX-2

The enzyme activity is measured using a chromogenic assay based on the oxidation of N,N,N',N'-tetramethyl-p-phenylenediamine (TMPD) during the reduction of PGG<sub>2</sub> to PGH<sub>2</sub> by COX-2 (Copeland et al. (1994) Proc. Natl. Acad. Sci. 91, 11202-11206).

Recombinant human COX-2 is purified from Sf9 cells as previously described (Percival et al (1994) Arch. Biochem. Biophys. 15, 111-118). The assay mixture (180  $\mu$ L) contains 100 mM sodium phosphate, pH 6.5, 2 mM genapol X-100, 1  $\mu$ M hematin, 1 mg/mL gelatin, 80-100 units of purified enzyme (One unit of enzyme is defined as the amount of enzyme required to produce an O.D. change of 0.001/min at 610 nm) and 4  $\mu$ L of the test compound in DMSO. The mixture is pre-incubated at room temperature (22° C.) for 15 minutes prior to initiation of the enzymatic reaction by the addition of 20  $\mu$ L of a sonicated solution of 1 mM arachidonic acid (AA) and 1 mM TMPD in assay buffer (without enzyme or hematin). The enzymatic activity is measured by

estimation of the initial velocity of TMPD oxidation over the first 36 sec of the reaction. A non-specific rate of oxidation is observed in the absence of enzyme (0.007–0.010 O.D./min) and is subtracted before the calculation of the % inhibition.  $IC_{50}$  values are derived from 4-parameter least squares non-linear regression analysis of the log-dose vs % inhibition plot.

#### HUMAN WHOLE BLOOD ASSAY

##### Rationale

Human whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors. Studies have shown that normal human blood does not contain the COX-2 enzyme. This is consistent with the observation that COX-2 inhibitors have no effect on PGE<sub>2</sub> production in normal blood. These inhibitors are active only after incubation of human whole blood with LPS, which induces COX-2. This assay can be used to evaluate the inhibitory effect of selective COX-2 inhibitors on PGE<sub>2</sub> production. As well, platelets in whole blood contain a large amount of the COX-1 enzyme. Immediately following blood clotting, platelets are activated through a thrombin-mediated mechanism. This reaction results in the production of thromboxane B<sub>2</sub> (TxB<sub>2</sub>) via activation of COX-1. Thus, the effect of test compounds on TxB<sub>2</sub> levels following blood clotting can be examined and used as an index for COX-1 activity. Therefore, the degree of selectivity by the test compound can be determined by measuring the levels of PGE<sub>2</sub> after LPS induction (COX-2) and TxB<sub>2</sub> following blood clotting (COX-1) in the same assay.

##### Method

##### A. COX-2 (LPS-induced PGF<sub>2</sub> production)

Fresh blood is collected in heparinized tubes by venipuncture from both male and female volunteers. The subjects have no apparent inflammatory conditions and have not taken any NSAIDs for at least 7 days prior to blood collection. Plasma is immediately obtained from a 2 mL blood aliquot to use as blank (basal levels of PGE<sub>2</sub>). The remaining blood is incubated with LPS (100 pg/ml final concentration, Sigma Chem, #L-2630 from *E. coli*; diluted in 0.1% BSA (Phosphate buffered saline) for 5 minutes at room temperature. Five hundred  $\mu$ L aliquots of blood are incubated with either 2  $\mu$ L of vehicle (DMSO) or 2  $\mu$ L of a test compound at final concentrations varying from 10 nM to 30  $\mu$ M for 24 hours at 37° C. At the end of the incubation, the blood is centrifuged at 12,000 $\times$ g for 5 minutes to obtain plasma. A 100  $\mu$ L aliquot of plasma is mixed with 400  $\mu$ L of methanol for protein precipitation. The supernatant is obtained and is assayed for PGE<sub>2</sub> using a radioimmunoassay kit (Amersham, RPA#530) after conversion of PGE<sub>2</sub> to its methyl oximate derivative according to the manufacturer's procedure.

##### B. COX-1 (Clotting-induced TxB<sub>2</sub> production)

Fresh blood is collected into vacutainers containing no anticoagulants. Aliquots of 500  $\mu$ L are immediately transferred to siliconized microcentrifuge tubes preloaded with 2  $\mu$ L of either DMSO or a test compound at final concentrations varying from 10 nM to 30  $\mu$ M. The tubes are vortexed and incubated at 37° C. for 1 hour to allow blood to clot. At the end of incubation, serum is obtained by centrifugation (12,000 $\times$ g for 5 min.). A 100  $\mu$ L aliquot of serum is mixed with 400  $\mu$ L of methanol for protein precipitation. The supernatant is obtained and is assayed for TxB<sub>2</sub> using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

#### RAT PAW EDEMA ASSAY

##### Protocol

Male Sprague-Dawley rats (150–200 g) are fasted overnight and are given, po, either vehicle (1% methocel or 5% Tween 80) or a test compound. One hr later, a line is drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume ( $V_0$ ) is measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals are then injected subplantarily with 50  $\mu$ L of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500  $\mu$ g carrageenan per paw). Three hr later, the paw volume ( $V_3$ ) is measured and the increases in paw volume ( $V_3 - V_0$ ) are calculated. The animals are sacrificed by CO<sub>2</sub> asphyxiation and the absence or presence of stomach lesions scored. Data is compared with the vehicle-control values and percent inhibition calculated. All treatment groups are coded to eliminate observer bias.

#### NSAID-INDUCED GASTROPATHY IN RATS

##### Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of Cox-1 in the gastrointestinal tract. Rats are particularly sensitive to the actions of NSAIDs. In fact, rat models have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring fecal <sup>51</sup>Cr excretion after systemic injection of <sup>51</sup>Cr-labeled red blood cells. Fecal <sup>51</sup>Cr excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

##### Methods

Male Sprague Dawley rats (150–200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats are injected via a tail vein with 0.5 mL of <sup>51</sup>Cr-labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water ad lib. Feces are collected for a 48 h period and <sup>51</sup>Cr fecal excretion is calculated as a percent of total injected dose. <sup>51</sup>Cr-labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400 Ci of sodium <sup>51</sup>chromate for 30 min. at 37° C. At the end of the incubation, the red blood cells are washed twice with 20 mL HBSS to remove free sodium <sup>51</sup>chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20 Ci) is injected per rat.

#### PROTEIN-LOSING GASTROPATHY IN SQUIRREL MONKEYS

##### Rationale

Protein-losing gastropathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard non-steroidal anti-inflammatory drugs (NSAIDs). This can be quantitatively assessed by intravenous administration of <sup>51</sup>CrCl<sub>3</sub> solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.

##### Methods

Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocell or 5% Tween 80 in H<sub>2</sub>O vehicles, (3 mL/kg b.i.d.) or test compounds at doses from 1–100 mg/kg b.i.d. for 5 days. Intravenous <sup>51</sup>Cr (5 Ci/kg in 1 mL/kg phosphate buffer saline (PBS)) is administered 1 h after the last drug/vehicle dose, and feces collected for 24 h in a metabolism cage and assessed for excreted <sup>51</sup>Cr by gamma-counting. Venous blood is sampled 1 h and 8 h after the last drug dose, and plasma concentrations of drug measured by RP-HPLC.

#### Representative Biological Data

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined measuring the amount of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a putative inhibitor. The IC<sub>50</sub> values represent the concentration of putative inhibitor required to return PGE<sub>2</sub> synthesis to 50% of that obtained as compared to the uninhibited control.

The results for certain of the biological assays may be seen in Tables II, III and IV.

TABLE II

Example	Rat Paw Edema ED <sub>50</sub> (mg/kg)
1	0.14
2	2.4
6	7.65
25	0.74

TABLE III

Example	COX-2 (IC <sub>50</sub> )			COX-1 (IC <sub>50</sub> )		
	TMPD uM	CHO uM	HWB uM	U937 uM	CHO uM	HWB uM
1	1.1	0.02	0.063	0.99	>50	9.2
2	0.2	0.02	0.074	3.0	>50	23.0
3	1.0	0.04	0.18	1.0	>50	6.1
4	0.62	0.01	0.04	1	>50	5
5	3.3	0.02	0.04	0.3		
6	2.0	0.01	0.02	0.4		1.8
7	1.4	0.009		1		
8	4.6	0.02	<0.41	0.3		
9	0.5	0.19	0.90	>10		>100
10	4.9		18.6	>10		
11	0.6	0.09	1.53	>30	>50	
12	14.7	3.52	4.5	>10		
13	64.4	0.118	2.65	>10		
14	10.8	0.1	<0.04	>10	>50	58.3
15	0.22	0.81	>30	>10	>50	
16	1.8		2.6	>10		>90
17	>100		.30	>10		
18	5.51		>30	>30		
19b	16.9	0.57	0.84	>10	>50	>90
20	0.44	0.03	0.23	0.3	4.68	
21	0.47	0.23	1.04	>10		
22	0.2		9.66	>1		
23	1.33	.5	1.53	>30	>50	
24c	3.0	0.03	<0.41	>3		25.3
25	4.7	0.02	<0.41	3	24	
26	35	0.12	0.12	~10	>100	
27	14	0.41	2.3	>10	>100	
29	3.6	0.015	1.0	1		

TABLE IV

Example	COX-2 (IC <sub>50</sub> , μM)			COX-1 (IC <sub>50</sub> μM)	Rat Paw Edema ED <sub>50</sub> (mg/kg)
	TMPD	CHO	HWB	CHO	
32	2.0	0.02	0.08		
37	>100	0.27	1.0	>50	—
38	41	0.49	0.52	>50	—
39	3.3	0.92	0.08		
45	11	>5	1.8		—
48	33	0.04	0.08		—
49	7.8	0.2	0.61		—
51	>100	0.67	0.26		—
53	47	>5	3.0		—
55	43	1.8	1.2		—
56		>5	4.8		—
57	54	2.0	23		—
58	6.4	0.04	0.08	>50	0.32
108	3.7	0.02	0.03	>50	0.68
109	11	0.04	0.4	>50	0.8
110	11	>5	3.0		—
111	>100	>5	15		—
112	28	0.03	0.04		8.0
113	8.7	0.03	<0.41		—
115	2.2	0.18	0.9		—
116	15	0.34	<0.41		—
117	0.95	0.02	0.02		1.0
118	2.2	0.008	0.05		1.4
119	>100	0.47	<0.41		—
120	42		4.5		—
121	1.6	0.09	0.45		10
122	4.6	0.15	0.38		1.2
123	11	0.09	<0.41		—
124	6.3	0.03	<0.41		—
125	>100	>5			—
127	5.8	0.04	0.04		—
128	1.7	0.01	<0.41		5.0
129	5.4	0.15	<0.41		—
130	7.9	0.03	<0.41		—
133	7.1	0.04	<0.41		—
134		0.04	0.08		0.9
136			1.3		—
137		0.55	5.2		—
140		0.12	0.54		4.6
141			0.03	<0.41	—
143	3.1		<0.41		—
144	2.9		<0.41		—
146			0.10		—
147			0.11		—
148		0.01	0.14		1.2
149	5.6	0.02	0.07		0.9
150	2.1	0.01	0.02		—
31	7.5	0.37	0.66		—
50	24	0.09	0.24		—
159	25	0.07	0.26		—
160	3.20	0.35	3.6		—
161	>100	2.9	1.7		—
162	8.0	0.06	0.62		—
163	6.6	0.02	0.09		0.64
164	>100	0.20	0.55		2.0
165	>100	2.0	4.5		—
166	6.5	0.05	0.28		4.9
167		0.11	0.21		6.4
168	3.0	0.05	1.1	29	1.0
169	4.0	0.05	<0.41		4.6
170		0.33	2.0		—
171			0.46		—
173			<0.41		—
174	5.8	0.02	<0.41		1.6
175	9.5	0.05	2.3		—
176	2.2	0.03	0.08		—
177	6.5	0.04	<0.41		—
178		0.04	<0.41		—
179			2.7		—
180			0.41		—
181			<0.41		—
184		0.04	<0.41		—
185		0.39	2.2		—



TABLE IV-continued

Example	COX-2 (IC <sub>50</sub> , $\mu$ M)			COX-1 (IC <sub>50</sub> , $\mu$ M)	Rat Paw Edema ED <sub>50</sub>
	TMPD	CHO	HWB	CHO	(mg/kg)
186		1.4	6.5		—
188		0.02	0.09		—
189		0.05	0.28		—
191		0.98	4.3		—
192		0.02	<0.41		—
195		0.02	<0.41		—
196		0.04	0.48		—
197		0.02	<0.41		—
198		0.06	0.17		—
199		0.11	0.87		—
200		0.16	0.13		—
201	14	0.07	0.18		2.7
202	13	0.04	<0.41		5.4
203		0.17	0.94		—

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18–25° C.;
- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600–4000 pascals: 4.5–30 mm Hg) with a bath temperature of up to 60° C.;
- (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;
- (iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;
- (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;
- (vi) yields are given for illustration only;
- (vii) when given, NMR data is in the form of delta ( $\delta$ ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad;
- etc.: in addition "Ar" signifies an aromatic signal;
- (viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), M.P. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

## EXAMPLE 1

3-(3,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Methyl-1-(4-(methylthio)phenyl)propan-1-one

To a suspension of aluminum chloride (136 g, 1.02 mol) in chloroform (1.0 L) cooled to -10° C., was added dropwise isobutyrylchloride (115 mL, 1.10 mol). Then thioanisole (100 mL, 0.85 mol) was added dropwise. Upon completion of addition the reaction was allowed to proceed at r.t. for 1.5h. The reaction was cooled to 10° C. and quenched by

addition of water (750 mL). The organic layer was separated, washed with water (2x500 mL), saturated NaHCO<sub>3</sub> solution(2x500 mL), brine (1x500 mL), and then dried over Na<sub>2</sub>SO<sub>4</sub>. After concentration in vacuo., the resulting crude product crystallized upon standing under high vacuum for 30 min to give the title compound as a brown solid.

Step 2: 2-Hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one

To a solution of 2-methyl-1-(4-(methylthio)phenyl)propan-1-one (28.5 g, 147 mmol, Step 1), Aliquat 336 (11.0 mL, 24 mmol) and carbon tetrachloride (21 mL, 218 mmol) in toluene (43 mL) was added sodium hydroxide (12.9 g, pellets, 322 mmol). The reaction was stirred at 15° C. for 2h and then at r.t. for 16h. The reaction was diluted with water (100 mL), brine (100 mL) and EtOAc (300 mL). The aqueous phase was acidified with 1 N HCl and extracted with EtOAc (100 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product was purified by silica gel chromatography eluted with 15% EtOAc in hexane to give the title compound as a thick syrup.

Step 3: 2-Hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one

To a cold (4° C.) solution of 2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one (45.0 g, 214 mmol, Step 2) in t-butanol (500 mL) and CH<sub>2</sub>Cl<sub>2</sub> (500 mL) was added a solution of OXONE™ (194 g, 316 mmol) in water (1.4 L). The resulting suspension was stirred at r.t. for 18 h. The reaction was diluted with EtOAc (400 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2x250 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude product was dissolved in diethyl ether (250 mL), hexane was added (150 mL) and the product was swished for 2 h. The product was collected by filtration to give the title compound as a yellow solid.

Step 4: 3-(3,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

A solution of 3,4-difluorophenoxyacetic acid (0.51 g, 2.73 mmol), 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (0.5g, 2.1 mmol, Step 3), CMC (1.13 g, 2.73 mmol) and DMAP (15 mg, 0.10 mmol) in dichloromethane (12 mL) was stirred at r.t. for 18 hrs. Then, DBU (0.63 mL, 4.2 mmol) was added and the reaction mixture was refluxed for 3 h. After cooling to r.t. the mixture was extracted with ethyl acetate and washed successively with water, 1 N HCl and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. The residue was triturated in a mixture of ethyl acetate and hexane affording the title compound as a solid. M.P.: 93–95° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  1.77 (6H, s), 3.15 (3H, s), 6.93–6.97 (1H, m), 7.12–7.29 (2H, m), 7.92 (2H, d), 8.04 (2H, d). Analysis calculated for C<sub>19</sub>H<sub>16</sub>F<sub>2</sub>O<sub>5</sub>S: C, 57.86; H, 4.09; Found: C, 57.77; H, 4.28

## EXAMPLE 2

3-(3-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 3-fluorophenoxyacetic acid. M.P.: 136–138° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  1.79 (6H, s), 3.15 (3H, s), 6.85–6.94 (3H, M), 7.31–7.86 (1H, m), 7.93 (2H, d), 8.03 (2H,d).

## 105

## EXAMPLE 3

3-(3,5-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 3,5-difluorophenoxyacetic acid. M.P.: 159–161° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.80 (6H, s), 3.17 (3H, s), 6.78–6.84 (3H, m), 7.96 (2H, d), 8.06 (2H, d). Analysis calculated for C<sub>19</sub>H<sub>16</sub>F<sub>2</sub>O<sub>5</sub>S: C, 57.86; H, 4.09; Found: C, 57.66; H, 4.30

## EXAMPLE 4

3-Phenoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 3-Phenoxy-5,5-dimethyl-4-(4-(methylthio)phenyl)-5H-furan-2-one

Following the procedure described for example 1, Step 4, the title compound was prepared from phenoxyacetic acid and 2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one (example 1, Step 4).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.79 (6H, s), 2.51 (3H, s), 7.03–7.10 (3H, m), 7.30–7.37 (4H, m), 7.72 (2H, d).

Step 2: 3-Phenoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

The compound obtained in Step 1 (150 mg, 0.46 mmol) was stirred in dichloromethane (5 mL) with 3-chloroperoxybenzoic acid (250 mg, 1.38 mmol) for 18 hrs. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. The residue was triturated in Et<sub>2</sub>O to afford the title compound. M.P.: 135–136° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78 (6H, s), 3.14 (3H, s), 7.05–7.08 (3H, m), 7.28–7.30 (2H, m), 7.92 (2H, d), 8.01 (2H, d). Analysis calculated for C<sub>19</sub>H<sub>16</sub>O<sub>5</sub>S: C, 63.67; H, 5.06; S, 8.95; Found: C, 64.02; H, 5.10; S, 8.84

## EXAMPLE 5

3-(2,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Bromoacetic acid, 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester

To a 0° C. solution of 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (4.0 g, 16.5 mmol, example 1, Step 3) in dichloromethane (100 mL) was added pyridine (23.5 mL, 291 mmol) and bromoacetyl bromide (24.9 mL, 285.3 mmol) portionwise over 2 hrs. The reaction mixture was allowed to warm to r.t. and stirred for a further hour. The mixture was diluted with dichloromethane, washed with 1 N HCl, brine, filtered through cotton and the solvent was evaporated under vacuum. Purification by silica gel chromatography (40% EtOAc/Hex.) provided 3.50 g of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75 (6H, s), 3.20 (3H, s), 4.00 (2H, s), 8.05 (2H, m), 8.25 (2H, m).

Step 2: 2-(2,4-Difluorophenoxy)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one-2-yl ester

Sodium hydride, 60% dispersion (66 mg, 1.66 mmol), was rinsed with hexane, suspended in 7 mL of DMF and cooled to 0° C. To this suspension was added 2,4-difluorophenol (170 μL, 1.79 mmol). After 5 minutes at 0° C., 2-bromoacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (Step 1) (233 mg, 1.79 mmol) was added and the reaction mixture was stirred for 30 minutes. Dichloromethane was added and the mixture was washed with 1N HCl and the organic solvent was evaporated

## 106

under vacuum. The residue was dissolved in 25% EtOAc/Et<sub>2</sub>O and washed with 1N NaOH, water (2x) brine and dried over MgSO<sub>4</sub>. After filtration and evaporation of the solvent under vacuum 470 mg of the title compound was obtained.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75 (6H, s), 3.20 (3H, s), 4.80 (2H, s), 6.60 (1H, m), 6.75 (1H, m), 7.00 (1H, m), 8.05 (2H, m), 8.20 (2H, m).

Step 3: 3-(2,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a solution of 2-(2,4-difluorophenoxy)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one-2-yl ester (Step 2) (470 mg, 1.14 mmol) in acetonitrile (7 mL) was added DBU (187 μL, 1.25 mmol) and the resulting solution was heated at 50° C. for 20 minutes. After cooling to r.t. dichloromethane was added and the mixture was washed with 1 N HCl, brine, filtered over cotton and the solvent evaporated under vacuum. Purification by silica gel chromatography followed by a swish in EtOAc/Et<sub>2</sub>O afforded 122 mg of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.70 (6H, s), 3.15 (3H, s), 6.90 (1H, m), 7.10 (1H, m), 7.30 (1H, m), 7.85 (2H, m), 8.00 (2H, m).

## EXAMPLE 6

3-(4-Chlorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 4-chlorophenoxyacetic acid. M.P.: 113–114° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.77 (6H, s), 3.15 (3H, s), 7.11 (2H, d), 7.31 (2H, d), 7.91 (2H, d), 8.04 (2H, d)

## EXAMPLE 7

3-(3,4-Dichlorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 3,4-dichlorophenoxyacetic acid. M.P.: 144–145° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78 (6H, s), 3.15 (3H, s), 7.12–7.15 (1H, m), 7.35–7.36 (1H, s), 7.49 (1H, d), 7.92 (2H, d), 8.04 (2H, d).

## EXAMPLE 8

3-(4-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 4-fluorophenoxyacetic acid.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.76 (6H, s), 3.14 (3H, s), 7.02–7.13 (4H, m), 7.91 (2H, d), 8.01 (2H, d).

## EXAMPLE 9

3-(4-Fluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 1, the title compound was prepared from 4-fluorophenylthioacetic acid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.55 (6H, s), 3.08 (3H, s), 6.85 (2H, m), 7.26 (2H, m), 7.35 (2H, d), 7.94 (2H, d)

## EXAMPLE 10

3-(3,5-Difluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a mixture of 3,5-difluorothiophenol (1.0 g) and methyl bromoacetate (1.2 g) in methanol (20 mL) was added 2 mL of a solution of NaOH (0.69 mL of 10N in 3 mL of water), the mixture was stirred for 1 h, then 2 mL of 10N NaOH was added and the mixture stirred for another hour.

The solvent was evaporated under vacuum, the residue taken in water and washed with Et<sub>2</sub>O, then acidified with 1N HCl and extracted with ether. The ether extract was washed with water, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum giving 850mg of 3,5-difluorophenylthioacetic acid. This acid was reacted as in Step 1 to afford the title compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.60 (6H, s), 3.10 (3H, s), 6.60–6.80 (3H, m), 7.45 (2H, d), 8.00 (2H, d).

#### EXAMPLE 11

3-Phenylthio-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from phenylthioacetic acid. M.P.: 98–114° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.61 (6H, s), 3.16 (3H, s), 7.21–7.30 (5H, m), 7.61 (2H, d), 7.96 (2H, d). Analysis calculated for C<sub>19</sub>H<sub>18</sub>O<sub>4</sub>S<sub>2</sub>: C, 60.94; H, 4.84; S, 17.12; Found: C, 61.01; H, 4.90; S, 16.94

#### EXAMPLE 12

3-(N-Phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Phenylaminoacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester

Following the procedure described in example 13 Step 1 but using aniline the title compound was obtained.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.70 (6H, s), 3.15 (3H, s), 3.95 (2H, br s), 5.15 (1H, br s), 6.40 (2H, m), 6.55 (1H, m), 7.00 (2H, m), 8.00 (2H, m), 8.25 (2H, m).

Step 2: 3-N-Phenylamino-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described in example 13 Step 2 but using 2-phenylaminoacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester the title compound was obtained.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.65 (6H, s), 3.05 (3H, s), 6.70 (3H, m), 6.95 (2H, m), 7.25 (1H, br s), 7.50 (2H, m), 7.75 (2H, m).

#### EXAMPLE 13

3-(N-Methyl-N-phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-(N-Phenyl-N-methylamino)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester

To a solution of 2-bromoacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (example 5, Step 1) (1.0 g, 2.75 mmol) in toluene (2.5 mL) was added N-methylaniline (3.0 mL, 27.5 mmol) and the resulting solution was heated at 115° C. for 16 hrs. After cooling to r.t. the reaction mixture was washed with brine and filtered through cotton. Purification by silica gel chromatography provided 850 mg of the title compound.

Step 2: 3-(N-Methyl-N-phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a solution of 2-(N-phenyl-N-methylamino)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (700 mg, 1.80 mmol) in acetonitrile (3 mL) was added DBU (2.7 mL, 18.0 mmol) and the resulting solution was heated at 60° C. for 1 h. After cooling to r.t. dichloromethane was added and the mixture was washed with 1N HCl, brine and filtered through cotton and the solvent was evaporated under vacuum. Purification by silica gel chromatography followed by swish in EtOAc/Hex. afforded 266 mg of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.70 (6H, s), 3.05 (3H, s), 3.15 (3H, s), 6.70 (1H, m), 6.80 (2H, m), 7.10 (2H, m), 7.65 (2H, m), 7.90 (2H, m)

#### EXAMPLE 14

3-Cyclohexyloxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Bromo-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one

To a solution of 2-methyl-1-(4-(methylthio)phenyl)propan-1-one (example 1, Step 1) (417.94 g) in ethyl acetate (1.2 L) and cyclohexane (1.7 L) was added bromine (110 mL) portionwise. After stirring for 10 min the mixture was washed with water, saturated sodium bicarbonate and brine.

To this mixture was then added sodium tungstate (6.7 g), Aliquat 336 (25 g) and water (200 mL). The mixture was then heated to 50° C. and hydrogen peroxide (30%, 600 mL) was added slowly. Ethyl acetate and water were then added to the mixture and the organic layer separated, washed with water, dried over sodium sulfate, filtered and the title compound crystallized and was collected by filtration.

Step 2: 2-Cyclohexyloxyacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester

A solution of 2-cyclohexyloxyacetic acid (1.74g, 11 mmol), 2-bromo-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (3.05 g, 10 mmol) and diisopropylethylamine (2.20 g, 17 mmol) in 30 mL of ethanol was refluxed for 15 h. The solvent was evaporated and the residue dissolved in water and extracted with EtOAc, washed with 5% HCl, saturated sodium bicarbonate, brine and dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. Purification by silica gel chromatography afforded 3.0 g of the title compound.

Step 3: 3-Cyclohexyloxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

A solution of the ester from the previous step (492 mg, 1.29 mmol) and DBU (1 mL) in 5 mL of acetonitrile was heated at reflux for 15 h. To the cooled solution was added 5% HCl and the mixture was extracted with EtOAc, washed with a saturated solution of ammonium chloride and dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. Purification by silica gel chromatography afforded the title compound. M.P.: 143–144° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.20–1.35 (3H, m), 1.40–1.50 (3H, m), 1.66 (6H, s), 1.60–1.70 (2H, m), 1.85–1.95 (2H, m), 3.20 (3H, s), 4.85 (1H, m), 8.00–8.10 (4H, m) Analysis calculated for C<sub>19</sub>H<sub>24</sub>O<sub>5</sub>S: C, 62.62; H, 6.64; Found: C, 62.28; H, 6.57

#### EXAMPLE 15

3-Phenylthio-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

At 0° C., triethylamine (335 μL) was added to a solution of thiophenoxyacetic acid (161 mg) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (272 mg, WO 9500501, example 9, Step 1) in 5 mL of acetonitrile and the mixture was stirred at 0° C. for 1 h. The reaction mixture was then cooled to –20° C. and DBU (265 μL) was added. The mixture was stirred for 30 min. at –20° C. and was quenched by addition of 1N HCl. The product was extracted with EtOAc, dried over sodium sulfate and partially purified by silica gel chromatography. The impure product was recrystallized from EtOAc/Hexane to afford the title compound as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.10 (3H, s), 5.25 (2H, s), 7.24–7.38 (5H, m), 7.93 (2H, d), 8.03 (2H, d). Analysis calculated for C<sub>17</sub>H<sub>14</sub>O<sub>4</sub>S<sub>2</sub>: C, 58.94; H, 4.07; Found: C, 58.88; H, 4.18

#### EXAMPLE 16

3-Benzyl-5,5-4-(4-(methylsulfonyl)phenyl)-5H-2-one

Step 1: 3-Phenylpropanoic acid 2-methyl-1-(4-(methylthio)phenyl)propan-1-on-2-yl ester

To a –30 ° C. solution of 2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one (1.05 g, example 1, Step

2) in dichloromethane (20 mL) was added 3-phenylpropionyl chloride (1.68 g) in dichloromethane (10 mL) followed by pyridine (791 mg) and the mixture was allowed to warm up slowly to 25° C. and stirred for 12 h. Ethyl acetate was added to the mixture and it was washed with 1N HCl, brine, dried over magnesium sulfate filtered and the solvent was evaporated under vacuum. Purification by silica gel chromatography afforded 1.36 g of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.65 (6H, s), 2.50 (3H, s), 2.55–2.65 (2H, t), 2.75–2.85 (2H, t), 7.10–7.40 (7H, m), 7.90–8.00 (2H, d)

Step 2: 3-Benzyl-5,5-dimethyl-4-(4-(methylthio)phenyl)-5H-furan-2-one

To a 0° C. solution of the ester from the previous step (1.14 g) in DMF (10 mL) and THF (2 mL) was added sodium hydride (120 mg of 80% dispersion) and the mixture was stirred for 2 h at 25° C. Then it was poured over icy 1N HCl and extracted with ethyl acetate, the organic layer was washed with water, brine, dried over MgSO<sub>4</sub> and the solvent evaporated under vacuum. The residue was purified by silica gel chromatography affording 596 mg of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.50 (6H, s), 2.55 (3H, s), 3.50 (2H, s), 7.05–7.30 (7H, m), 7.35–7.40 (2H, d)

Step 3: 3-Benzyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a 0° C. solution of the lactone from the previous step (596 mg) in dichloromethane (10 mL) and methanol (5 mL) was added portionwise MMPP (2×590 mg) and the mixture was allowed to slowly warm-up to 25° C. After 2 h. at 25° C. the mixture was partitioned between dichloromethane and water, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. The residue was swished in ether to yield 530 mg of the title compound.

Analysis calculated for C<sub>20</sub>H<sub>20</sub>O<sub>4</sub>S: C, 67.40; H, 5.65; Found: C, 67.28; H, 5.78

#### EXAMPLE 17

3-(3,4-Difluorophenylhydroxymethyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Using a procedure similar to the Steps 1, 2 and 3 of example 19 but using 3,4-difluorobenzaldehyde as an electrophile the title compound was obtained.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.45 (6H, s), 3.15 (3H, s), 5.00 (1H, hs), 5.50 (1H, hs), 6.45–6.55 (2H, d), 7.00–7.30 (3H, m), 7.95–8.05 (2H, d).

#### EXAMPLE 18

3-(3,4-Difluorobenzoyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Using a procedure similar to Step 4 of example 19 and using the compound obtained in example 17, the title compound was obtained.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75 (6H, s), 3.10 (3H, s), 7.35–7.45 (1H, m), 7.65–7.75 (2H, d), 7.75–7.90 (2H, m), 7.95–8.05 (2H, d).

#### EXAMPLE 19

3-Benzoyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: Acetic acid 2-methyl-1-(4-methylthiophenyl)propan-1-on-2-yl ester

To a 0° C. solution of 2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one (150 g, example 1, Step 2), DBU (217 g) and DMAP (7 g) in dichloromethane (850 mL) was added acetyl chloride (112.2 g) dropwise and the mixture was stirred for 6 h. at 25° C. More DBU (32.5 g)

was added and the mixture was stirred an additional 16 h. The reaction mixture was poured over 2N HCl (800 mL) and the organic layer was separated, washed with a saturated solution of NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. The residue was swished in Et<sub>2</sub>O, then 25% ethyl acetate in hexane, then filtered and dried giving 74 g of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.60 (6H, s), 1.90 (3H, s), 2.55 (3H, s), 7.30 (2H, d), 8.00 (2H, d).

Step 2: 5,5-Dimethyl-4-(4-(methylthio)phenyl)-5H-furan-2-one

To a 0–5° C. solution of the ester from the previous step (74 g) in DMF (1.2 L) was added NaH (9 g, 80% dispersion) portionwise and the mixture was stirred for 3 h. Saturated aqueous NH<sub>4</sub>Cl was added slowly. The mixture was then partitioned between ethyl acetate and water, the organic layer was washed with water, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. The residue was swished in 30% ethyl acetate/hexane to yield the title compound (38 g).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.70 (6H, s), 2.55 (3H, s), 6.40 (1H, s), 7.40 (2H, d), 7.70 (2H, d).

Step 3: 5,5-Dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(phenylhydroxymethyl)-5H-furan-2-one

To a –78° C. solution of the lactone (702 mg) obtained in the previous step in THF was added 0.67M LDA (9.25 mL) and the mixture was reacted for 5 min. Benzoyl chloride (913 mg) was then added at –78° C. and after 15 min the mixture was poured over icy 1N HCl. The organic material was extracted with ethyl acetate, washed with brine, dried with MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. The residue was dissolved in dichloromethane (10 mL) and methanol (10 mL) and the solution cooled to 0° C. MMPP (4.9 g) was added and the mixture warmed and stirred at 25° C. for 2 h. The mixture was poured over icy water and the organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. The residue was purified by silica gel chromatography to yield 190 mg of compound which was dissolved in methanol (2 mL) and THF (1 mL), cooled to 0° C. and a catalytic amount of NaOH was added. The mixture was poured in icy water and extracted with ethyl acetate, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum.

Step 4: 3-Benzoyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

The residue was dissolved in acetone (3 mL), and Jones' reagent (3M, 150 μL) was added. The mixture was stirred for 1 h. then poured over icy water and extracted with ethyl acetate, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. The residue was swished in ether to yield the title compound (123 mg).

Analysis calculated for C<sub>20</sub>H<sub>18</sub>O<sub>5</sub>S: C, 64.85; H, 4.84; Found: C, 64.63; H, 5.23

#### EXAMPLE 20

4-(4-(Methylsulfonyl)phenyl)-3-phenoxy-1-oxaspiro[4.4]non-3-en-2-one

Using a procedure similar to the one used in example 1 but using (1-hydroxycyclopentyl)-(4-(methylsulfonyl)phenyl)methanone from example 21, Step 3 and phenoxy-acetic acid the title compound was obtained.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.80–2.30 (8H, m), 3.04 (3H, s), 6.95–7.35 (5H, m), 7.75 (2H, d), 7.95 (2H, d).

## EXAMPLE 21

4-(4-(Methylsulfonyl)phenyl)-3-phenylthio-1-oxaspiro[4.4]non-3-en-2-one

Step 1: Cyclopentyl-(4-(methylthio)phenyl)methanone

To a suspension of anhydrous aluminum chloride (9.3 g, 69.6 mmol) in 58 mL  $\text{CHCl}_3$  at  $0^\circ\text{C}$ . was added dropwise cyclopentanecarbonyl chloride (10.0 g, 75.4 mmol), followed by thioanisole (7.21 g, 58.0 mmol). The ice bath was removed and the mixture was stirred at room temperature for 2 h. Water (200 mL) was added with cooling, the layers were separated and the aqueous layer was extracted with  $\text{CHCl}_3$  (3x50 mL). The combined aqueous layers were dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was chromatographed on silica gel (4% EtOAc/hexane) to give 11.9 g of the title ketone (93%).

$^1\text{H NMR}$  ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  7.94 (d, 2H), 7.36 (d, 2H), 3.79 (q, 1H), 2.56 (s, 3H), 2.00–1.71 (m, 4H), 1.70–1.50 (m, 4H).  
Step 2: (1-Hydroxycyclopentyl)-(4-(methylthio)phenyl)methanone

To a solution of the ketone from Step 1 (7.2 g, 32.7 mmol) in 4.7 mL  $\text{CCl}_4$  and 9.6 mL toluene was added Aliquat 336 (2.11 g, 5.20 mmol) and powdered NaOH (2.88 g, 71.9 mmol) and the mixture was stirred for 16 h at r.t. To the brown mixture was added 100 mL of 5% aq. HCl and extracted with EtOAc (4x100 mL). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. Chromatography on silica gel (20% EtOAc/hexane) gave 5.4 g of the title compound as a white wax solid (70%).

$^1\text{H NMR}$  ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  8.11 (d, 2H), 7.31 (d, 2H), 4.63 (s, 1H, disappears by  $\text{D}_2\text{O}$  wash), 2.56 (s, 3H), 2.24 (m, 2H), 1.89 (m, 4H), 1.71 (m, 2H).

Step 3: (1-Hydroxycyclopentyl)-(4-(methylsulfonyl)phenyl)methanone

The sulfide obtained in Step 2 (56 g) was dissolved in dichloromethane (800 mL) and methanol (200 mL) and treated with MMPP (139 g) and stirred for 3 h. The organic layer was diluted with dichloromethane, washed with water and brine, dried over  $\text{MgSO}_4$ , filtered and the solvent evaporated to afford the title compound.

Step 4: 4-(4-(Methylsulfonyl)phenyl)-3-phenylthio-1-oxaspiro[4.4]non-3-en-2-one

The hydroxyketone from the previous step was reacted with phenylthioacetic acid as in the procedure for example 1, Step 4 to afford the title compound.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.70–2.05 (8H, m), 3.06 (3H, s), 7.10–7.25 (5H, m), 7.35 (2H, d), 7.90 (2H, d).

## EXAMPLE 22

4-(2-Oxo-3-phenylthio-1-oxa-spiro[4.4]non-3-en-4-yl)benzene-sulfonamide

To a solution of 1-(hydroxycyclopentyl)-(4-methylthiophenyl)methanone (52 g, example 21, Step 2) in  $\text{CH}_2\text{Cl}_2$  (400 mL) and methanol (200 mL) at  $0^\circ\text{C}$ . was added portionwise MMPP (61 g). After stirring for 3 h the reaction mixture was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to dryness to provide the sulfoxide intermediate which (75.6 g) was dissolved in TFAA (100.0 mL) and refluxed for 3 h. The mixture was cooled to  $0^\circ\text{C}$ . and 10N NaOH (24 mL), was added dropwise and under nitrogen. After vigorous stirring for 0.5 h, acetic acid (100 mL) and water (20 mL) was added. The mixture was cooled to  $0^\circ\text{C}$ . and chlorine gas was bubbled for 20 min. The excess chlorine was removed under vacuum and the mixture was poured over icy water and extracted with ethyl acetate. The extracts were washed with water, saturated  $\text{NaHCO}_3$  and brine. The organic layer was cooled to  $0^\circ\text{C}$ . and t-butylamine (10 mL) was added and stirred for 1 h. The

reaction mixture was diluted with water and neutralized with 6N HCl, washed with brine, dried over  $\text{MgSO}_4$ , filtered and the solvent evaporated under vacuum. The residue was swished in ether. This hydroxyketone (325 mg) was then reacted as in example 1, Step 4 using phenylthioacetic acid (200 mg) to give an intermediate (300 mg) which was stirred in dichloromethane (2 mL) and trifluoroacetic acid (8 mL) for 18 h. The solvents were then evaporated under vacuum and the residue was recrystallized from ethanol to afford the title compound.

$^1\text{H NMR}$  ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.65–2.20 (8H, m), 6.68 (2H, br s), 7.25 (5H, m), 7.55 (2H, d), 7.95 (2H, d).

## EXAMPLE 23

3-(4-Fluorobenzyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Using a procedure similar to the one for example 16 but using 3-(4-fluorophenyl)propionyl chloride the title compound was obtained.

$^1\text{H NMR}$  ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.50 (6H, s), 3.15 (3H, s), 4.45 (2H, s), 7.05–7.15 (2H, m), 7.50–7.60 (2H, d), 7.85–7.95 (2H, m), 7.95–8.05 (2H, d).

## EXAMPLE 24

3-(3,4-Difluorophenoxy)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Bromo-1-(4-(methylsulfonyl)phenyl)propan-1-one

Following a procedure similar to the one used in example 1, Step 1 but using propionyl chloride, 1-(4-(methylsulfonyl)phenyl)propan-1-one was obtained. A solution of this compound (163.4 g) in chloroform (2.2 L) was then cooled to  $0^\circ\text{C}$ . and treated with bromine (40 mL in 200 mL  $\text{CHCl}_3$ ) and concentrated HBr (10 mL). The reaction mixture was washed with water, saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered and the solvent evaporated under vacuum. The residue was swished in ethyl acetate: hexane 1:1 to give the title compound (191 g).

Step 2: 5-Hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenylthio-5H-furan-2-one

To a mixture of 2-bromo-1-(4-(methylsulfonyl)phenyl)propan-1-one (6.0 g, 20.6 mmol) and thiophenoxyacetic acid (3.8 g, 22.6 mmol) in acetonitrile (60 mL) was added triethylamine (4.0 mL, 28.8 mmol). The mixture was stirred at r.t. for 3 h. T.L.C. showed no bromoketone remaining and DBU (4.0 mL) was added. The mixture was stirred at r.t. for 1 h., then air was bubbled through the mixture for another hour. After dilution with water, the mixture was extracted with EtOAc. The EtOAc extract was washed with 1N aqueous HCl, brine, dried over  $\text{MgSO}_4$ , filtered and the solvent evaporated under vacuum. The residue was swished in  $\text{Et}_2\text{O}$  to give the title compound (6.0 g) as a pale yellow powder.

$^1\text{H NMR}$  ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.68 (3H, s), 3.16 (3H, s), 6.86 (1H, s), 7.35 (5H, m), 7.78 (2H, d), 7.98 (2H, d).

Step 3: 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenylthio-5H-furan-2-one

The alcohol (2.5 g, 6.6 mmol) from the previous step was dissolved in methanol (100 mL), THF (20 mL) and concentrated HCl (5 mL) and heated at  $70^\circ\text{C}$ . for 24 h. After cooling to  $0^\circ\text{C}$ . the precipitate formed was filtered, washed with methanol and dried under vacuum to give the title compound (2.0 g) as a yellow solid.

$^1\text{H NMR}$  ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.65 (3H, s), 3.15 (3H, s), 3.40 (3H, s), 7.18–7.40 (5H, m), 7.88 (2H, d), 7.98 (2H, d).

Step 4: 3-(3,4-Difluorophenoxy)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a solution of the compound obtained in the previous step (2.0 g, 5.1 mmol) in dichloromethane (100 mL) at r.t. was added mCPBA (4.0 g, Aldrich 57–86%, 16 mmol). The mixture was stirred at r.t. for 3 h and more mCPBA (2.0 g) was added. After stirring for another hour the mixture was washed with 1N NaOH, brine, dried and concentrated under vacuum to yield a disulfone as a white foam (2.0 g). To a solution of 3,4-difluorophenol (2.0 g, 14.9 mmol) in DMF was added 10N NaOH (1 mL, 10 mmol). After 30 min. a solution of the above disulfone (2.0 g, 4.7 mmol) in DMF was added. The mixture was heated at 80–85° C. for 1.5 h. After cooling the mixture was diluted with water, extracted with EtOAc, the organic extracts were washed with 1N NaOH, 1N HCl, brine, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. Purification by silica gel chromatography afforded the title compound as a white solid (600 mg).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.86 (3H, s), 3.16 (3H, s), 3.40 (3H, s), 6.95–7.40 (3H, m), 8.08 (2H, d), 8.16 (2H, d).

#### EXAMPLE 25

3-(5-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a mixture of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (1.0 g, 3.13 mmol, prepared similarly to the compound of example 5, Step 1) and 5-chloro-2-pyridinol (0.41 g, 3.16 mmol) in CH<sub>3</sub>CN (20 mL) was added DBU (1.5 mL, 10.0 mmol) at r.t. The mixture was stirred for 1 h, then heated at 65–70° C. for 3h. The volatile solvents were removed in vacuo. The residue was chromatographed over silica gel and eluted with hexane:EtOAc (1:1) to yield a colorless oily residue which was swished in Et<sub>2</sub>O to provide the title compound as a white powder (230 mg).

<sup>1</sup>NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.80 (6H, s), 3.20 (3H, s), 7.18 (1H, d), 7.94 (3H, m), 8.06 (2H, d), 8.19 (1H, d).

#### EXAMPLE 26

(2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 25, the title compound was prepared from 2-hydroxypyridine.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78 (6H, s), 3.15 (3H, s), 7.00–7.20 (2H, m), 7.80–8.20 (6H, m).

#### EXAMPLE 27

3-(6-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 25, the title compound was prepared from 2-hydroxy-6-methylpyridine.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75 (6H, s), 3.14 (3H, s), 6.85 (1H, d), 7.00 (1H, d), 7.70 (1H, t), 7.90 (2H, d), 8.00 (2H, d).

#### EXAMPLE 28

3-(3-Isoquinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 25, the title compound was prepared from 3-hydroxyisoquinoline.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.80 (6H, s), 3.14 (3H, s), 7.40–8.10 (9H, m), 9.00 (1H, s).

#### EXAMPLE 29

3-(4-(Methylsulfonyl)phenyl)-2-phenoxy-cyclopent-2-enone  
Step 1: 1-(4-(Methylthio)phenyl)-5-phenoxy-penta-1,4-dione

To a mixture containing 1-phenoxybut-3-en-2-one (1.0 g) (A. G. Schultz, R. D. Lucci, W. Y. Fu, M. H. Berger, J.

Erhardt and W. K. Hagmann, J. Amer. Chem. Soc. 100, 2150, (1978)), 4-(methylthio)benzaldehyde (0.62 g) and triethylamine (0.343 mL) in 1,4-dioxane (20 mL) was added 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (110 mg). After stirring 4h. at 100° C. the reaction mixture was extracted with EtOAc, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. The residue was purified by silica gel chromatography (20% EtOAc/Hexane) to afford 140 mg of the title compound as an oil.

Step 2: 3-(4-(Methylthio)phenyl)-2-phenoxy-cyclopent-2-enone

To the diketone of Step 1 (120 mg) in methanol (80 mL) was added DBU (0.1 mL). The resulting mixture was heated at 60° C. for 18 h. The methanol was then evaporated and to the crude mixture was added saturated aqueous ammonium chloride, the mixture was then extracted with EtOAc, the organic layer was dried over MgSO<sub>4</sub>, filtered, and the solvent evaporated under vacuum. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to afford the title compound.

Step 3: 4-(4-(Methylsulfonyl)phenyl)-2-phenoxy-cyclopent-2-enone

To the compound obtained in Step 2 (60 mg) in dichloromethane (4.5 mL) and methanol (2.4 mL) was added Oxone® (450 mg) in water (1 mL) and the reaction mixture was stirred for 1 h. Water was added to the mixture which was then extracted with dichloromethane, the organic layers were combined and dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum. Purification by silica gel chromatography afforded the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 2.65 (2H, t), 3.15 (3H, s), 3.20 (2H, t), 7.05–7.35 (5H, m), 8.10 (4H, m).

#### EXAMPLE 30

2-(3,4-difluorophenoxy)-3-(4-(methylsulfonyl)phenyl)-cyclopent-2-enone

Step 1: 3,4-Difluorophenoxy-methyl vinyl ketone

To a suspension of 3,4-difluorophenoxy acetic acid (5.00 g, 25.7 mmol) lithium salt in DME (20 mL) was added to a 1M THF solution of vinyl magnesium bromide (38 mmol). After a period of 18 h, the resulting clear solution was poured over 1N HCl (67 mL). The aqueous phase was then extracted with Et<sub>2</sub>O. The ethereal phase was washed with H<sub>2</sub>O, 1M K<sub>2</sub>CO<sub>3</sub> then H<sub>2</sub>O. After drying over MgSO<sub>4</sub> and evaporation an orange oil was obtained and used as such for the next step.

Step 2: 2-(3,4-difluorophenoxy)-3-(4-(methylsulfonyl)phenyl)-cyclopent-2-enone

Following the procedure described in Example 29 but using the compound obtained in the previous step the title compound was obtained.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 2.60 (2H, t), 3.15 (3H, s), 3.20 (2H, t), 6.90 (1H, m), 7.15 (1H, m), 7.25 (1H, Q), 8.10 (4H, 2d).

#### EXAMPLE 32

3-(5-Benzothiophenyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 5-hydroxybenzothiophene.

M.P.: 150–152° C. <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78 (6H, s), 3.08 (3H, s) 7.17 (1H, dd), 7.32 (1H, d), 7.56 (1H, d), 7.68 (1H, d), 7.92–7.99 (5H, m).

## 115

## EXAMPLE 37

5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(pyridin-4-yloxy)-5H-furan-2-one

To a R.T. solution of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (318 mg, 1 mmol) in DMF (5 mL) was added 4-pyridone (380 mg, 4.0 mmol) followed by DBU (623 mg, 4.1 mmol) and the mixture was slowly warmed up to R.T. for 16 hrs and then to 60–70° C. for 1–2 hours. The mixture was cooled to R.T. and poured on icy dilute NH<sub>4</sub>Cl and EtOAc; the organic layer was separated and the aqueous further extracted with EtOAc. The combined organic layers were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and the solvents were removed in vacuo. The residue was purified on silica gel chromatography (1/1, Acetone/toluene) to provide the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.8(6H,s), 3.15(3H,s), 7.05–7.15(2H,m), 7.9–8.1(4H,AB), 8.4–8.5(2H,m).

## EXAMPLE 38

5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(pyridin-3-yloxy)-5H-furan-2-one

To a R.T. solution of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (318 mg, 1 mmol) in DMF (5 mL) was added 3-hydroxypyridine (95 mg, 1 mmol) followed by DBU (623 mg, 4.1 mmol) and the mixture was slowly warmed up to R.T. for 16 hrs and then to 60–70° C. for 1–2 hours. The mixture was cooled to R.T. and poured on icy dilute NH<sub>4</sub>Cl and EtOAc; the organic layer was separated and the aqueous further extracted with EtOAc. The combined organic layers were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and the solvents were removed in vacuo. The residue was purified on silica gel chromatography (1/1, Acetone/toluene) to provide the title compound.

Analysis calculated for C<sub>18</sub>H<sub>17</sub>NO<sub>5</sub>S: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.01; H, 4.81; N, 3.90.

## EXAMPLE 39

3-(2-Methyl-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 5-hydroxy-2-methylpyridine M.P.: 168–169° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.77 (6H, s), 2.41 (3H, s), 3.15 (3H, s), 7.14 (1H, d), 7.37 (1H, dd), 7.93 (2H, d), 8.03 (2H, d), 8.25 (1H, d).

## EXAMPLE 44

3-(2-Fluoro-4-trifluoromethyl)phenoxy-4-(4-methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

Following the procedure for Example 25, the title compound was prepared from 2-fluoro-4-trifluoromethylphenol; m.p.: 192–194.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78 (6H, s), 3.16 (3H, s), 7.49 (2H, m), 7.64 (1H, d, J=11.6 Hz), 7.95 (2H, d, J=8.3 Hz), 8.05 (2H, d, J=8.5 Hz). Analysis calculated for C<sub>20</sub>H<sub>16</sub>F<sub>4</sub>O<sub>5</sub>S: C, 54.06; H, 3.63; Found: C, 54.09, H, 3.72.

## EXAMPLE 45

3-(5-Chloro-2-pyridylthio)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 5-chloro-2-mercaptopyridine.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.70(6H, s), 3.20(3H, s), 7.38 (1H, d), 7.72(3H, m), 8.06(2H, d), 8.42(1H, m).

## 116

## EXAMPLE 46

2-(3,5-Difluorophenoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone

Using similar protocol described for Example 29 but using 1-(3,5-difluorophenoxy)but-3-en-2-one the title compound was obtained.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 2.60 (2H, t), 3.15 (3H, s), 3.20 (2H, t), 6.60 to 6.85 (3H, m), 8.10 (4H, 2d).

## EXAMPLE 47

3-(2-Pyrimidinoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxypyrimidine hydrochloride.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78(6H, s), 3.18(3H, s), 7.34 (1H, t), 7.40(2H, d), 8.06(2H, d), 8.68(2H, d).

## EXAMPLE 48

3-(3-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-Hydroxy-3-methylpyridine

To 10% aqueous H<sub>2</sub>SO<sub>4</sub> (90 mL) at 0° C. was added 2-amino-3-methylpyridine (6.0 g, 56 mmol). The mixture was stirred at 0° C. for 30 mins and a solution of 4N aqueous NaNO<sub>2</sub> (13 mL) was added dropwise over a period of 15 min. The mixture was further stirred and warmed to rt over 1 h. The pH was then adjusted to 6–7 by the addition of 10N aqueous NaOH. The whole mixture was then extracted with CHCl<sub>3</sub>, washed with H<sub>2</sub>O, dried (anhydrous MgSO<sub>4</sub>) and concentrated in vacuo. The crude material was swished with Et<sub>2</sub>O to give the title compound (2.5 g, 42%) as a white solid.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 2.02(3H, s), 6.10(1H, m), 7.30 (2H, m).

Step 2: 3-(3-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-3-methylpyridine.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78(6H, s), 2.30(3H, s), 3.14 (3H, s), 7.05(1H, m), 7.65(1H, m), 7.95(3H, m), 8.02(2H, d).

## EXAMPLE 49

3-(3-Chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 2-chloro-5-hydroxypyridine. M.P.: 176–177° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.79 (6H, s), 3.16 (3H, s), 7.70 (1H, m), 7.96 (2H, d), 8.05 (2H, d), 8.33 (1H, d), 8.40 (1H, d).

## EXAMPLE 51

3-(3-(1,2,5-Thiadiazolyl)oxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

Following the procedure for example 25, the title compound was prepared from 3-hydroxy-1,2,5-thiadiazol; m.p.: 127–129.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78 (6H, s), 3.16 (3H, s), 7.92 (2H, d, J=8.6 Hz), 8.06 (2H, d, J=8.6 Hz), 8.49 (1H, s).

Analysis calculated for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub>: C, 49.17; H, 3.85; N, 7.65; Found: C, 49.01, H, 3.84; N, 7.37.

## EXAMPLE 52

3-(5-Isoquinolinoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 5-hydroxyisoquinoline.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.80(6H, s), 3.10(3H, s), 7.38 (1H, d), 7.55(1H, t), 7.85(1H, d), 7.95(4H, m), 8.04(1H, d), 8.58(1H, d), 9.30(1H, s).

## EXAMPLE 53

3-(6-Amino-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-6-aminopyridine.

M.P.: 165–166° C. <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.74 (6H, s), 3.14 (3H, s), 5.52 (2H, s, br), 6.17 (1H, d), 6.24 (1H, d), 7.41 (1H, t), 7.90 (2H, d), 8.02 (2H, d).

## EXAMPLE 54

3-(3-Chloro-4-fluorophenoxy)-4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

Following the procedure for Example 25, the title compound was prepared from 3-chloro-4-fluorophenol; m.p.: 130–132° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.76 (6H, s), 3.14 (3H, s), 7.10 (1H, m), 7.24 (1H, t, J=9Hz), 7.30 (1H, m), 7.92 (2H, d, J=8.5 Hz), 8.03 (2H, d, J=8.5 Hz).

## EXAMPLE 55

3-(6-Quinolinoxyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 6-hydroxyquinoline. M.P.: 171–172° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.82 (6H, s), 3.08 (3H, s), 7.46 (1H, m), 7.53–7.60 (3H, m), 7.95–8.01 (5H, m), 8.23 (1H, m), 8.80 (1H, m).

## EXAMPLE 56

3-(5-Nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-5-nitropyridine.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.80(6H, s), 3.18(3H, s), 7.38 (1H, d), 7.92(2H, d), 8.05(2H, d), 8.66(1H, m), 9.05(1H, m).

## EXAMPLE 57

3-(2-Thiazolylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 2-mercaptothiazole. M.P.: 174–176° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.67 (6H, s), 3.19 (3H, s), 7.59 (1H, d), 7.68 (1H, d), 7.74 (2H, d), 8.07 (2H, d).

## EXAMPLE 58

3-(3-Fluoro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 5-fluoro-2-hydroxypyridine. M.P.: 157–159° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.76 (6H, s), 3.16 (3H, s), 7.16 (1H, m), 7.74 (1H, m), 7.92 (2H, d), 8.03 (2H, d), 8.07 (1H, m).

## EXAMPLE 109A

5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

Step 1: 5,5-Dimethyl-3-hydroxy-4-(4-methylsulfonylphenyl)

To a 0° C. solution of the alcohol of Example 1, Step 3 (29.5 g, 122 mmol) in CH<sub>3</sub>CN (350 mL) were added

pyridine (25 mL) and acetoxyacetyl chloride (25 g, 183 mmol). After a period of 7 h at r.t., DBU (31 mL) was added to the reaction mixture. After a period of 1 h at 80° C., a second portion of DBU (35 mL) was added. The reaction mixture was kept at 80° C. for 18 h. The reaction mixture was allowed to cool to r.t. The mixture was poured onto ice-water (2.5 L) containing 100 mL of concentrated HCl. The brown solid was collected and dissolved in hot acetonitrile and was filtered through a plug of silica. The solvent was evaporated and the resultant solid was swished in EtOAc to give the title compound (21.2 g, 62%).

Step 2: 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

To a suspension of the alcohol of Step 1 (18.16 g, 64.4 mmol) in benzene (350 mL) were added an excess of 2-iodopropane (19.3 mL) and Ag<sub>2</sub>CO<sub>3</sub> (53.3 g, 1.06 mmol). After stirring for 18 h, the reaction mixture was filtered and the filtrate was washed with hot EtOAc. After evaporation, the crude compound was purified by flash chromatography (35% to 40% EtOAc/hexane, followed by addition of 5% CH<sub>2</sub>Cl<sub>2</sub>) to provide 19 g of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.25 (6H, d), 1.70 (6H, s), 3.20(3H,s), 5.20(1H,septet), 8.05 (4H, s).

## EXAMPLE 109b

5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

Step 1: 5,5-Dimethyl-3-hydroxy-4-(4-methylsulfonylphenyl)-5H-furan-2-one

To a 0° C. solution of the alcohol of Example 1, Step 3 (14.0 g, 57.8 mmol) in CH<sub>3</sub>CN (180 mL) were added pyridine (10.0 mL) and acetoxyacetyl chloride (12.7 g, 93.0 mmol) after a period of 7 h at r.t., DBU (15.0 mL) was added to the reaction mixture. After a period of 1 h at 80° C., a second portion of DBU (20.0 mL) was added. The reaction mixture was kept at 80° C. for 18 h. The reaction mixture was allowed to cool to r.t. The mixture was diluted with EtOAc (500 mL) and H<sub>2</sub>O (500 mL) and acidified with 6NHCl. After the addition of brine (100 mL), the aqueous phase was extracted 2 times with EtOAc. The organic phase was evaporated to provide a brown residue. To the solid was added a 2:1 mixture of CH<sub>2</sub>Cl<sub>2</sub>-toluene (150 mL). The solid was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub>-toluene to provide 7.0 g of the title compound.

Step 2: 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

To a suspension of the alcohol of Step 1 (100 mg, 0.354 mmol) in benzene (5.0 mL) were added an excess of 2-iodopropane (105 mL) and Ag<sub>2</sub>CO<sub>3</sub> (294 mg, 1.06 mmol). After a period of 18 h at 45° C., the reaction mixture was filtered over celite and washed with CH<sub>2</sub>Cl<sub>2</sub>. After evaporation, the crude compound was purified by flash chromatography (35% to 40% EtOAc) to provide 70 mg of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.25 (6H, d), 1.70 (6H, s), 3.20 (3H, s), 5.20 (1H, Septet), 8.05 (4H, s).

Alternatively compound 109 may be prepared in the following manner:

Step A 1: 2-Methyl-1-(4-(thiomethyl)phenyl)propan-1-one  
A 500 mL flask was charged under N<sub>2</sub> with 34.5 g (259 mmol) of AlCl<sub>3</sub> and 100 mL of ODCB. The vigorously stirred slurry was cooled to 8° C. and isobutyryl chloride (28.6 mL, 261 mmol) was added over 30 min., keeping the temperature at 10–15° C.

The addition of isobutyryl chloride was slightly exothermic.

The AlCl<sub>3</sub>/isobutyryl chloride complex was aged at 7° C. for 30 min. Efficient cooling was applied and thioanisole



(31.2 g) was added to the reaction mixture over 120 min., maintaining an internal temperature of 8–13° C.

The addition of thioanisole was very exothermic. After the addition of about half of thioanisole a heavy yellow precipitate formed. The precipitation was accompanied by an exotherm. Gaseous HCl is formed in the reaction, so that the effluent gas stream should be scrubbed with aqueous NaOH before release into the atmosphere.

The reaction was warmed to 16° C. over 1 h.

The reaction mixture was a thick yellow slurry at this point. HPLC analysis of a quenched (EtOAc/H<sub>2</sub>O) aliquot indicated completion of reaction.

The reaction mixture was cooled to 10° C. and 160 mL of 5% aqueous HCl were added over 45 min.

The addition was extremely exothermic and especially the initial addition required careful temperature monitoring.

The biphasic mixture was vigorously stirred for 60 min. The lower organic phase was removed.

A quantitative assay of the organic phase indicated a 98% yield.

Step A 2: 2-Bromo-2-methyl-1-(4-(thiomethyl)phenyl)propan-1-one

A 500 mL flask was charged with the solution of the compound from step A 1 (246 mMol). Approximately 10% of the bromine (1.3 mL, 26 mMol) were added and the reaction mixture was stirred until the red color had dissipated after 45 min. The remainder of the Br<sub>2</sub> (12 mL) was added over 60 min.

The reaction was exothermic and the temperature rose to ca. 32° C.

Gaseous HBr was released from the reaction, thus the effluent gas stream was scrubbed with aqueous NaOH before release into the atmosphere.

The reaction mixture was aged for 2 h at 30° C. when HPLC analysis indicated completion of the reaction.

Addition of a slight excess of Br<sub>2</sub> leads to the partial oxidation of the sulfide to the sulfoxide.

The reaction was quenched by the addition of 160 mL H<sub>2</sub>O and the resulting 182.0 mL of organic phase were used directly for the oxidation (next step) (95% assay yield).

Step A 3: 2-Bromo-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one

To a solution of the compound from the previous step in ODCB in a 500 mL reaction vessel with heating jacket, reflux condenser and bottom valve was added under N<sub>2</sub> a solution of Na<sub>2</sub>WO<sub>4</sub> (0.45 g, 1.4 mMol) and Aliquat 336 (2.2 g, 5.4 mMol) in 3.0 mL H<sub>2</sub>O. The heterogeneous reaction mixture was heated with vigorous stirring to 35° C. and ca. 3.0 mL of H<sub>2</sub>O<sub>2</sub> (30%) were added.

The oxidation was extremely exothermic. After an induction period of ca. 3 min. the temperature rose quickly to 50–65° C.

The remainder of the H<sub>2</sub>O<sub>2</sub> (36 mL) was added over 1 h. At the end of the addition HPLC analysis indicated completion of the reaction.

The reaction mixture was heated to 80° C., the lower organic phase was removed and cooled to 6° C. over 1 h.

The product precipitated at ca. 50° C. without seeding.

The slurry was filtered and washed with 25.0 mL of ODCB and 30.0 mL of hexane and three times with 20.0 mL of 60° C. H<sub>2</sub>O. After drying 37.8 g of the title compound (97% yield, ca. 91% overall yield from thioanisole) were obtained as a white powder.

Step A 4: Isopropoxyacetic acid

A 500 mL vessel fitted with a mechanical stirrer, thermocouple probe, and nitrogen inlet is charged with 200 mL of IPA (K.F. 220 µg/mL) and sodium hydroxide (6.0 g, 0.145

mol). The mixture was heated at reflux until the solid sodium hydroxide dissolved.

A homogeneous solution is obtained after reflux for 3 h.

The solution was cooled at ~70° C. and toluene (15.0 mL) was added. It was distilled until ~100 mL of distillate was collected. A mixture of IPA/toluene (85:15, 100 mL) was added and ~0.1 L of liquid was distilled off (repeated 3x). At the end of distillation (~0.4 L of distillate collected), the solution was diluted with IPA to a volume of ~300 mL.

The distillate is assayed to determine the amount of water removed. If the water removed is <75% of the theoretical amount (K.F. of IPA+that in NaOH+1 equiv generated), the distillation should be continued. The solution was then cooled at 60–70° C. and sodium chloroacetate (15.9 g, 0.134 mol) was added in portions over 5 min. No exotherm is observed during the addition.

The mixture was heated at reflux for 3 h and a sample of the slurry was taken for assay.

The reaction is followed by <sup>1</sup>HNMR. An aliquot (~0.2 mL) of the mixture is taken and evaporated to dryness. The residue is dissolved in D<sub>2</sub>O for <sup>1</sup>HNMR measurement. The reaction is considered completed when the starting material is <3% vs. product.

The reaction was quenched by addition of 60.0 mL of water and concentrated under reduced pressure (150–200 mbar, 50–60° C.) until ~250 mL of distillate was collected. More water was added (40.0 mL) and the solution was distilled at normal pressure until the hatch temperature reached ~103° C. (~100 mL of solution left, ~300 mL of solvent removed). The solution was cooled at 10–20° C. and neutralized by addition of conc. hydrochloric acid (12.5 mL, 0.15 mol).

External cooling may be needed during the addition of acid. The final pH should be <2.3, preferably ~2.

t-Butyl methyl ether (80.0 mL) was added. The aqueous solution was saturated with sodium chloride (~9.0 g) and the two-phase mixture was agitated for 0.5 h at 10–15° C. The layers were separated and the aqueous layer was back extracted with 2x60.0 mL of t-butyl methyl ether. The organic layers were combined and washed with 2x10.0 mL of saturated aqueous sodium chloride.

The pH of the 2nd brine wash should be >2.5.

The organic solution was dried over 4A molecular sieves (10.0 g) for 14 h and filtered. The sieves were washed with 3x15.0 mL of t-butyl methyl ether. t-Butyl methyl ether was removed under reduced pressure (~200 mbar, 45–50° C.). Isopropoxyacetic acid was obtained as a slightly yellow liquid.

Yield: 11.8 g, 75% yield.

Step A 5: 2-(isopropoxy)acetic acid 2-methyl-1-(4-methylsulfonyl)phenylpropan-1-one-2-yl ester

A 100 mL flask was sequentially charged with dry ethanol (45.0 mL, K.F. <100 µg/mL), isopropoxyacetic acid (2.32 g), diisopropylethylamine (4.85 mL) and the bromosulfone (step A 3)(5.0 g). The mixture is heated to reflux until the bromosulfone is not detected (HPLC, reaction time 12–14 hours).

The reaction is considered complete when the bromosulfone is <0.05 A % vs. product.

After the reaction was complete, the solution was allowed to cool and seeded at 42° C. Crystallization initiated immediately and the mixture was cooled to 1° C. and aged 1 hr. The product ester is filtered and washed with ethanol (0° C. 5.0 mL wash). After drying in a vacuum oven, the white crystalline title compound was used as is in the next step.

Yield: 4.15 g.

Step A 6: 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

## 121

A 1L flask was sequentially charged with dry acetonitrile (320 mL, K.F.<100 µg/mL), isopropyl trifluoroacetate (30.1 g, 0.193 mol), and DBU (36.70 g, 0.24 mol). The solution was stirred at ~20 ° C. for 15 min and the ester from Step AS (55.0 g, 0.161 mol) was added. The solution was heated at reflux under nitrogen and the progress of the reaction was followed by HPLC.

The reaction is considered complete when the intermediate peaks are <0.2 A % vs. product.

After the reaction was complete, the solution was cooled at ~40 ° C. and filtered (1 µ in-line capsule). The solution was then concentrated at 40–50 ° C. under reduced pressure until ~0.20 L of distillate was collected. Water (350 mL) was added slowly at ~45 ° C. After ~130 mL of water was added, the solution turned cloudy (40–45 ° C.) and ~0.02 g of crystalline title compound was added as the seed. The mixture was aged for 30 min and the remaining water was added. The mixture was aged at ~20 ° C. for 6 h then filtered. The cake was washed with 2×65 mL of 1:4 MeCN/water and 3×65 mL of water. The title product was air dried and dried in vacuo (35° C., 200 mBar).

Yield: ~48.0 g, 92%.

## EXAMPLE 110

3-(3-Trifluoromethyl)phenoxy-4-(4-methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 3-trifluoromethylphenol.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.79 (6H, s), 3.14 (3H, s), 7.41 (3H, m), 7.55 (1H, m), 7.95 (2H, dd, J=2, 6.6 Hz), 8.03 (2H, dd, J=2, 6.7 Hz). Analysis calculated for C<sub>20</sub>H<sub>17</sub>F<sub>3</sub>O<sub>5</sub>S: C, 56.34; H, 4.02; Found: C, 56.21, H, 4.01.

## EXAMPLE 111

5,5-Dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(piperidine-1-carbonyl)-5H-furan-2-one.

Step 1: 5,5-Dimethyl-4-(4-(methylsulfonyl)phenyl)-2-oxo-2,5-dihydrofuran-3-carboxylic acid ethyl ester

A mixture of 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (2.87 g, 11.8 mmol), ethyl hydrogen malonate (2.02 g, 15.3 mmol), CMC (6.51 g, 15.4 mmol) and DMAP (0.35 g, 2.8 mmol) was dissolved in 100 mL of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred for 14 h at room temperature, then DBU (4 mL, 27 mmol) was added, stirred 1 h, then partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 1M HCl. The organic layer was washed with brine, filtered through cotton and evaporated. Purification by flash chromatography (90% ether/Hex) provided 2.50 g of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 8.09 (2H, m), 7.68 (2H, m), 4.05 (2H, q), 3.16 (3H, s), 1.58 (6H, s), 0.96 (3H, t).

Step 2: 5,5-Dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(piperidine-1-carbonyl)-5H-furan-2-one

To a room temperature solution of piperidine (284 mg, 3.33 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added trimethylaluminum (2M in hexane, 1.7 mL, 3.4 mmol). After 15 min, the product from Step 1 (310 mg, 0.92 mmol) was added in one portion and the mixture was heated to reflux for 20h. The resulting solution was cooled and poured into 1M HCl (gas evolution). The organic layer was washed with brine, filtered through cotton and evaporated. Purification by flash chromatography (80% EtOAc/Hex) provided 175 mg of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 8.08 (2H, m), 7.80 (2H, m), 3.49 (2H, m), 3.35 (2H, m), 3.17 (3H, s), 1.65 (6H, s), 1.55 (2H, m), 1.40 (4H, m).

## 122

## EXAMPLE 112

5,5-Dimethyl-3-(2-butoxy)-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Step 1: 5,5-Dimethyl-3-(2-butoxy)-4-(4-methylsulfonylphenyl)-5H-furan-2-one

To a suspension of the alcohol of Example 109, Step 1 (300 mg, 1.06 mmol) in benzene (20.0 mL) were added 2-iodobutane (300 µL) and Ag<sub>2</sub>CO<sub>3</sub> (400 mg, 3.27 mmol). After a period of 4 h at 45° C., the reaction mixture was filtered over celite and washed with CH<sub>2</sub>Cl<sub>2</sub>. After evaporation, the crude product was purified by flash chromatography (35% EtOAc in Hexane) to give 150 mg of the title compound as a white solid.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.09 (3H, t), 1.20 (3H, d), 1.65 (6H, s), 3.20 (3H, s), 5.00 (1H, m), 8.00 (4H, s).

## EXAMPLE 113

5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(3-pentoxo)-5H-furan-2-one

Step 1: Pentyl-3-oxoacetic acid

To a solution of 3-pentanol (17.6 g, 200 mmol) in benzene (200 mL) was added NaH (6.0 g, 400 mmol). After 1 h at r.t., chloroacetic acid sodium salt (25.6 g, 200 mmol) was added to the previous mixture. After a period of 2 hr. at reflux, the reaction mixture was poured in H<sub>2</sub>O and acidified with HCl. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub>, filtered over silicic acid (30% EtOAc in Hexane). After evaporation of the solvents the title compound was purified by distillation (5.0 g).

Step 2: Pentyl-3-oxoacetic acid 2-methyl-1-(4-methylsulfonylphenyl)propan-1-one-yl ester

The title compound was obtained using similar protocol as described for Example 1 Step 3.

Step 3: 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(3-pentylxy)-5H-furan-2-one.

To a solution of the ester of Step 2 (500 mg, 1.35 mmol) in DMF (2.5 mL) was added NaH (50 mg, 1.6 mmol). The reaction mixture was heated gently to give an orange mixture. After standard extractive workup procedure (EtOAc), the crude mixture was purified by flash chromatography (35% EtOAc in hexane) to afford 115 mg of the title compound by filtration in Et<sub>2</sub>O/hexane.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.85 (6H, t), 1.60 (4H, m), 1.65 (6H, s), 3.20 (3H, s), 4.90 (1H, quintet), 8.05 (4H, s).

## EXAMPLE 115

2-(5-Chloro-2-pyridinoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-one

Using similar protocol described for Example 29 but using 1-(5-chloropyridyl-2-oxy)but-3-en-2-one the title compound was obtained.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 2.50 (2H, t), 2.80 (3H, s), 3.10 (2H, t), 7.10 (1H, d), 7.30 (2H, d), 7.80 (2H, d), 7.85 (1H, dd), 8.05 (1H, d).

## EXAMPLE 116

3-(4-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-4-methylpyridine.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.76 (6H, s), 2.36 (3H, s), 3.15 (3H, s), 6.90 (1H, s), 6.98 (1H, d), 7.89 (2H, d), 7.98 (1H, d), 8.02 (2H, d).

## 123

## EXAMPLE 117

(5R)-3-(3,4-Difluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-(S)-t-butyl-5-(R)-ethyl-4-hydroxy-5-methyl-4-(4-methylthio)phenyl-1,3-dioxolan-4-one

To a solution of 4-bromothiobanisole (27.3 g, 134 mmol) in 300 ml of anhydrous THF at  $-72^{\circ}\text{C}$ . was added 2.5 M n-BuLi in hexanes (54 ml, 135 mmol) at such a rate as to maintain the internal temperature below  $-55^{\circ}\text{C}$ . and the mixture was stirred at  $-72^{\circ}\text{C}$ . for an hour. A solution of 2-(S)-t-butyl-5-(R)-ethyl-5-methyl-1,3-dioxolan-4-one (16.8 g, 90 mmol, *Tetrahedron*, 1984, 40, 1313) in 50 ml of THF was added dropwise and the mixture was stirred at  $-72^{\circ}\text{C}$ . for 15 minutes. Acetic acid (13 ml) was then added slowly and the mixture stirred for another 10 min. at  $-72^{\circ}\text{C}$ . The reaction was quenched with 25% aq.  $\text{NH}_4\text{OAc}$  at  $-72^{\circ}\text{C}$ . and allowed to warm up to r.t. The title product was extracted in i-PrOAc, dried over  $\text{Na}_2\text{SO}_4$  and purified by flash chromatography on silica with EtOAc/hexane 2.5 and 5% to yield 22.4 g (80%) of a white solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , mixture of 2 diastereoisomers 1.8:1) d 0.58, 1.52, 1.68 and 2.05 (2H, 4m), 0.70 and 1.36 (3H, 2s), 0.73 and 0.98 (3H, 2T), 1.00 (9H, 2s), 2.47 (3H, 2s), 2.47 and 2.57 (1H, 2s, 1H), 4.80 and 5.00 (1H, 2s), 7.20 (2H, 2d), 7.45 (2H, 2d).

Step 2: 2-(R)-hydroxy-2-methyl-1-(4-(methylthio)phenyl)-1-butanone

A mixture of the product of step 1 (32.0 g, 103 mmol), p-toluenesulfonic acid (900 mg) and 35 ml of water was heated to reflux for an hour. The title product was extracted in 200 mL of EtOAc and the solution used as such in the next step.

Step 3: 2-(R)-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-1-butanone-1-one

To the product of Step 2 in 200 ml of EtOAc in an ice bath (to maintain the temperature of the reaction below  $25^{\circ}\text{C}$ .) was added 100 ml of t-BuOH, 2.3 g of Aliquat 336® and a solution of 73.1 g of Oxone® (238 mmol  $\text{KHSO}_5$ ) in 450 ml of water and the mixture was stirred at r.t. overnight. It was then neutralized with 10N NaOH. The title product was extracted in i-PrOAc, dried over  $\text{Na}_2\text{SO}_4$ , and purified by flash chromatography on silica with EtOAc/toluene 20 & 40% to yield 23.8 g of a colorless oil. NMR experiments with the chiral shift reagent Eu (hfc)<sub>3</sub> indicated an enantiomeric excess superior than 94%.  $[\alpha]_D^{25} = -11.2^{\circ}$  (c=0.8,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.87 (3H, t), 1.57 (3H, s), 1.93 (2H, m), 3.07 (3H, s), 3.53 (1H, s), 8.00 (2H, d), 8.13 (2H, d).

Step 4: (5R)-3-(3,4-Difluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 1, step 4, the title compound was prepared from 3,4-difluorophenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one.

$[\alpha]_D^{25} = +9.4^{\circ}$  (c 0.9, acetone).

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  0.95 (3H, t), 1.80 (3H, s), 2.12 (2H, q), 3.18 (3H, s), 6.95 (1H, m), 7.14 (1H, m), 7.30 (1H, m), 7.95 (2H, d), 8.06 (2H, d).

## EXAMPLE 118

(5R)-3-(4-Chlorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 117, the title compound was prepared from 4-chlorophenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  0.93 (3H, t), 1.78 (3H, s), 2.12 (2H, q), 3.15 (3H, s), 7.11 (2H, d), 7.35 (2H, d), 7.92 (2H, d), 8.03 (2H, d).

## 124

## EXAMPLE 119

3-(2-Methyl-3-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 3-hydroxy-2-methylpyridine.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.77 (6H, s), 2.48 (3H, s), 3.14 (3H, s), 7.08 (1H, m), 7.33 (1H, d), 7.93 (2H, d), 8.02 (2H, d), 8.16 (1H, m).

## EXAMPLE 120

3-(4-Methyl-5-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A mixture of 3-hydroxy-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one (1.5 g, 5.33 mmol, Example 109 step 1), 2-chloro-4-methyl-5-nitropyridine (1.0 g, 5.8 mmol) and powdered KOH (300 mg, 5.4 mmol) in DMF (20 mL) was heated at  $100^{\circ}\text{C}$ . for 12 h. After cooling to r.t., the mixture was diluted with  $\text{H}_2\text{O}$ , extracted with EtOAc. The EtOAc extract was washed with brine, dried (anhydrous  $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was swished with EtOH to give the title compound as a pale yellow solid (1.7 g, 77%).

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.80 (6H, s), 2.68 (3H, s), 3.16 (3H, s), 7.20 (1H, s), 7.90 (2H, d), 8.05 (2H, d), 8.85 (1H, s).

## EXAMPLE 121

3-(5-Chloro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 3-(5-Amino-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A mixture of 3-(4-methyl-5-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one (1.4 g, 3.3 mmol), iron powder (1.5 g, 27 mmol) and  $\text{NH}_4\text{Cl}$  (150 mg) in 67% aqueous EtOH (45 mL) was refluxed for 1 h. The hot mixture was filtered through celite. Volatile solvent was evaporated in vacuo. The residue was suspended in water, filtered and dried under vacuum to give the title compound as a brown powder (1.2 g, 94%).

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.72 (6H, s), 2.20 (3H, s), 3.15 (3H, s), 4.42 (2H, brs), 6.75 (1H, s), 7.50 (1H, s), 7.90 (2H, d), 8.00 (2H, d).

Step 2: 3-(5-Chloro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

To a suspension of 3-(5-amino-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one (600 mg, 1.6 mmol) in 6M aqueous HCl (3 mL) at  $0^{\circ}\text{C}$ . was added dropwise a solution of 4M aqueous  $\text{NaNO}_2$  (450 mL, 1.8 mmol). The solution became clear and then precipitate formed. After stirring for 30 min, the diazotization mixture was added to a solution of CuCl (300 mg, 3.0 mmol) in concentrated HCl (2 mL) at  $0^{\circ}\text{C}$ ., then heated to  $70-80^{\circ}\text{C}$ . for 10 min, cooled to r.t. and diluted with  $\text{H}_2\text{O}$  and dried under vacuum. Recrystallization from EtOH-Acetone yielded the title compound as a light yellow solid (360 mg, 57%).

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.76 (6H, s), 2.40 (3H, s), 3.16 (3H, s), 7.10 (1H, s), 7.90 (2H, d), 8.05 (2H, d), 8.10 (1H, s).

## EXAMPLE 122

3-(5-Fluoro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

To a suspension of 3-(5-amino-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one (650 mg, 1.68 mmol, Example 121 step 1) in 6M aqueous HCl (4 mL) at  $0^{\circ}\text{C}$ . was added dropwise a solution of 4M aqueous  $\text{NaNO}_2$  (450 mL, 1.8 mmol). After stirring at  $0^{\circ}\text{C}$ .

## 125

for 30 min, 60% aqueous HPF<sub>6</sub> (2 mL) was added and the mixture was further stirred for 30 min. The precipitate was collected, washed with H<sub>2</sub>O and dried under vacuum to give 850 mg of diazonium salt.

The diazonium salt was then heated with a propane torch until the compound started to decompose. The dark brown residue was dissolved in acetone and chromatographed over silica gel, eluted with hexanes:EtOAc(2:3) to provide the title compound as a pale yellow solid (100 mg, 17%).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.72(6H, s), 2.34(3H, s), 3.16(3H, s), 7.02(1H, m), 7.90(2H, d), 7.94(1H, s), 8.02(2H, d).

## EXAMPLE 123

3-(3-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 3-(3-Nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A mixture of 3-hydroxy-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one (1.5 g, 5.3 mmol), 2-chloro-3-nitropyridine (1.0 g, 6.3 mmol) and powdered KOH (320 mg, 5.7 mmol) in DMF (20 mL) was heated at 100° C. for 12 h. After cooling to r.t., the mixture was diluted with H<sub>2</sub>O, extracted with EtOAc. The EtOAc extract was washed with brine, dried (anhydrous MgSO<sub>4</sub>) and concentrated in vacuo. Chromatography over silica gel and elution with hexanes:EtOAc(1:1) gave a solid residue. The residue was swished with EtOH to provide 1.6 g (73%) of title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.82(6H, s), 3.18(3H, s), 7.50(1H, m), 8.00(4H, m), 8.50(1H, m), 8.60(1H, d).

Step 2: 3-(3-Amino-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A mixture of 3-(4-methyl-4-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one (1.5 g, 3.7 mmol), iron powder (1.5 g, 27 mmol) and NH<sub>4</sub>Cl (150 mg) in 67% aqueous EtOH (45 mL) was refluxed for 1 h. The hot mixture was filtered through celite. Volatile solvent was evaporated in vacuo. The residue was suspended in water, filtered and dried under vacuum to give the title compound as a brown powder (1.4 g, quantitative).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.76(6H, s), 3.18(3H, s), 4.88(2H, brs), 6.86(1H, m), 7.10(1H, m), 7.35(1H, m), 7.98(4H, m).

Step 3: 3-(3-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

To a suspension of 3-(3-amino-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one (700 mg, 1.7 mmol) in 6M aqueous HCl (3 mL) at 0° C. was added dropwise a solution of 4M aqueous NaNO<sub>2</sub> (500 mL, 2.0 mmol). After stirring for 30 min, the diazotization mixture was added to a solution of CuCl (400 mg, 4.0 mmol) in concentrated HCl (2 mL) at 0° C., then heated to 70–80° C. for 10 min, cooled to r.t., diluted with H<sub>2</sub>O and extracted with EtOAc. Chromatography over silica gel and elution with hexanes:EtOAc(1:1) to give a solid residue (100 mg). Recrystallization from EtOH provided the pure title compound (90 mg, 13%).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.80(6H, s), 3.16(3H, s), 7.20(1H, m), 7.94(2H, d), 7.98(1H, m), 8.05(2H, d), 8.10(1H, m).

## EXAMPLE 124

3-(4-Fluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-propyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-1-pentanone and 4-fluorophenol.

## 126

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.94(3H, t), 1.38(2H, m), 1.78(3H, s), 2.05(2H, m), 3.14(3H, s), 7.08(4H, m), 7.92(2H, d), 8.02(2H, d).

## EXAMPLE 125

3-(Diethyl amino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-(diethyl amino) acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one-2-yl ester

To a room temperature solution of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one-2-yl ester (2.00 g, 6.27 mmol) in acetonitrile (10 mL) was added diethyl amine (1.62 mL, 15.7 mmol). The resulting solution was heated to 60° C. for 16 hours. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and water. The organic layer was separated, washed with brine, filtered through cotton and the solvent was evaporated under vacuum. Purification by silica gel chromatography (80% EtOAc/Hex.) provided 1.70 g of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.85 (6H, t), 1.70 (6H, s), 2.37 (4H, q), 3.15 (3H, s), 3.27 (2H, s), 8.00–8.07 (2H, m), 8.15–8.22 (2H, m).

Step 2: 3-(Diethyl amino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Sodium hydride, 60% dispersion (0.478 g, 11.96 mmol) was washed in hexane and suspended in DMF (5 mL). This suspension was added to a 0° C. solution of 2-(diethyl amino) acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one-2-yl ester (1.70 g, 4.78 mmol) in DMF (20 mL). The resulting mixture was warmed to RT for 15 minutes. The mixture was diluted with ethyl acetate and quenched with water. The organic layer was washed with brine, dried over MgSO<sub>4</sub> and concentrated to dryness. The residue was purified by swishing in ether/hexanes to give 500 mg of crystalline solid on filtration.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.95 (6H, t), 1.45 (6H, s), 3.07 (4H, q), 3.17 (3H, s), 7.65–7.70 (2H, m), 7.97–8.05 (2H, m).

## EXAMPLE 127

5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(3,5-dichloropyridin-2-yloxy)-5H-furan-2-one

To a R.T. solution of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (954 mg, 3 mmol, example 25) in acetonitrile (15 mL) was added 3,5-dichloro-2-pyridone (656 mg, 4.0 mmol) followed by DBU (2.28 g, 15 mmol) and the mixture was slowly warmed up to gentle reflux for 2 hours. The mixture was cooled to 25° C. the volatiles were removed in vacuo. The residue was purified on silica gel chromatography (1/1, EtOAc/Hexanes then 100% EtOAc) to provide the title compound.

Analysis calculated for C<sub>18</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>3</sub>S: C, 50.48; H, 3.53; N, 3.27. Found: C, 50.53; H, 3.49; N, 3.21.

## EXAMPLE 128

(5R)-3-(4-Bromophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 117, the title compound was prepared from 4-bromophenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenylbutan-1-one.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.93(3H, t), 1.78(3H, s), 2.12(2H, q), 3.15(3H, s), 7.05(2H, d), 7.50(2H, d), 7.94(2H, d), 8.05(2H, d).

## 127

## EXAMPLE 129

(5R)-3-(4-Methoxyphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenylbutan-1-one (prepared similarly to the compound of Example 5 step 1) and 4-methoxyphenol.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 0.92(3H, t), 1.75(3H, s), 2.08(2H, q), 3.14(3H, s), 3.74(3H, s), 6.83(2H, d), 6.97(2H, d), 7.89(2H, d), 7.99(2H, d).

## EXAMPLE 130

(5R)-3-(5-Chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Step 1: 2-(S)-t-butyl-5-(R)-methyl-5-(2,2,2-trifluoroethyl)-1,3-dioxolan-4-one

To a solution of lithium diisopropylamide (prepared from 13 ml of diisopropylamine and 54 ml of 1.6 M n-BuLi in hexanes in 200 ml of anhydrous THF at 0° C.) at -72° C. was added slowly 2-(s)-t-butyl-5-(s)-methyl-1,3-dioxolan-4-one (12.95 g, 81.9 mmol, *Tetrahedron*, 1984, 40, 1313) at such a rate as to maintain the internal temperature below -60° C. and the mixture was aged at -72° C. for an hour. 1,1,1-Trifluoro-2-iodoethane (25 g, 119 mmol) was added quickly, the reaction temperature increased to -45° C. and the mixture was aged at -72° C. for 45 min. and then allowed to warm up to -20° C. over 20 min. Saturated aq. NH<sub>4</sub>Cl was then added and the product was extracted in i-PrOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and distilled under reduced pressure to afford 7.51 g of a brown oil BP 90° C./20 mm Hg.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, mixture of distereoisomers 3.2:1) δ 0.97(9H, 2s), 1.50 and 1.54(3H, 2s), 2.59(2H, m), 5.22(1H, 2d).

Step 2: 2-(R)-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-4,4,4-trifluoro-1-butanone

Using the procedures of Example 117 step 1, 2 and 3, the product of Step 1 was converted to the title compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.68(3H, s), 2.72(1H, mn), 2.98(1H, m), 3.08(3H, s), 3.35(1H, brs, OH), 8.03(2H, d), 8.14(1H, d).

Step 3: (2R)-2-Chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-butan-1-one

A mixture of (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-1-butanone(5.2 g, 16.8 mmol), chloroacetic acid(2.0 g, 21 mmol), CMC(9.5 g, 22 mmol) and DMAP(100 mg) in CH<sub>2</sub>Cl<sub>2</sub>(50 mL) was stirred at r.t. for 2 h. TLC showed the esterification completed. The mixture was washed with H<sub>2</sub>O (2x), dried (anhydrous MgSO<sub>4</sub>) and concentrated in vacuo. Chromatography over silica gel and elution with hexanes:EtOAc (1:1) gave 6.0 g(92%) of the title compound as an oil.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.98(3H, s), 3.18(3H, s), 3.28(2H, m), 4.35(2H, m), 8.08(2H, d), 8.28(2H, d).

Step 4: (5R)-3-(5-Chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-butan-1-one and 5-chloro-2-pyridinol.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.94(3H, s), 3.16(3H, s), 3.24(2H, q), 7.20(1H, d), 7.95(1H, m), 7.98(2H, d), 8.04(2H, d), 8.16(1H, m).

## 128

## EXAMPLE 133

3-(5-Chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-propyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-1-pentanone (prepared in a fashion similar to that of the compound in example 1 step 1, 2 and 3) and 5-chloro-2-pyridinol.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 0.93(3H, t), 1.42(2H, m), 1.76(3H, s), 2.05(2H, m), 3.15(3H, s), 7.16(1H, d), 7.90(3H, m), 8.02(2H, d), 8.16(1H, m).

## EXAMPLE 134

3-(1-Cyclopropyl-ethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: (1-cyclopropyl-ethoxy)acetic acid

To a suspension of NaH (80% in oil) (15.7 g, 523 mmol) in THF (180 mL) at 0° C. were added bromoacetic acid (28.0 g, 203 mmol) and α-methylcyclopropane methanol (10.0 g, 116 mmol). The resulting mixture was then stirred at 70° C. After a period of 18 h, the reaction mixture was poured over cold H<sub>2</sub>O and the H<sub>2</sub>O phase was extracted once with Et<sub>2</sub>O. The water phase was acidified with HCl and extracted twice with Et<sub>2</sub>O. The ether was dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. The crude oil was then purified by flash chromatography (40% EtOAc in hexane to 40% EtOAc in Hexane+AcOH) to provide 5.0 g of the title compound.

Step 2: 2-(1-Cyclopropylethoxy)acetic acid 2-methyl-1-(4-methylsulfonyl)phenylpropan-1-one-2-yl ester

A mixture of (1-cyclopropyl-ethoxy) acetic acid (1.0 g, 6.90 mmol; Example 134, Step 1) 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (1.37 g, 5.76 mmol; Example 1, Step 3), CMC (8.90 g, 20.8 mmol) and DMAP (100 mg, 0.820 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was left at r.t. for a period of 18 h. The resulting mixture was partitioned between NH<sub>4</sub>OAc (20%) and CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. The resulting mixture was purified by flash chromatography (35% EtOAc in hexane) to provide 590 mg of the title compound.

Step 3: 3-(1-Cyclopropylethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

To a solution of 2-(1-cyclopropyl-ethoxy)acetic acid 2-methyl-1-(4-(methyl sulfonyl)phenyl) propan-1-one-2-yl ester (590 mg, 1.60 mmol; Example 134, Step 2) CH<sub>3</sub>CN (20 mL) were added isopropyl trifluoro acetate (294 mL, 2.07 mmol) and DBU (782 mg, 5.14 mmol). After a period of 18 h at 70° C. The reacting mixture was evaporated under reduced pressure and purified by flash chromatography (30% EtOAc in toluene) to provide 270 mg of the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.20 to 0.50(5H, m), 0.90(1H, m), 1.35(3H, d), 1.65(6H, s), 3.20(3H, s), 4.35(1H, quintet), 8.10(4H, m).

## EXAMPLE 136

5-Methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-(propoxy)-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for Example 109, using 2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-4-trifluorobutan-1-one the title compound was obtained.

Step 2: 3-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl-5-(2-trifluoroethyl)-5H-furan-2-one

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.30(6H, 2d), 1.80(3H, s), 3.15(3H, s), 3.15 to 3.40(2H, m), 5.30(1H, quintet), 8.10(4H, m).

## EXAMPLE 140

5(R)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

The title compound was prepared as described in Example 109, Step 2 using (5R)-5-ethyl-3-hydroxy-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one, which was prepared from the compound of Example 117, Step 3 following the procedure of Example 109, Step 1.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.75–0.83 (3H, m), 1.24–1.30 (6H, m), 1.67 (3H, s), 2.01–2.08 (2H, m), 3.18 (3H, s), 5.17–5.27 (1H, m), 8.00–8.07 (4H, m).

## EXAMPLE 141

5,5-Dimethyl-3-(2,2-dimethylpropyloxy)-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a mixture of 5,5-dimethyl-3-hydroxy-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one (500 mg, 1.77 mmol, Example 109, Step 1) in DMF (6 mL) were added NaH (65 mg, 1.2 eq.), and neopentyl iodide (585 μL). After a period of 18 h at 70 °C., the reaction mixture was diluted with EtOAc. The mixture was washed with H<sub>2</sub>O and the organic phase separated, dried over MgSO<sub>4</sub> and evaporated under reduced pressure. The resulting oil was purified by flash chromatography to provide the title compound (124 mg) as a white solid after precipitation with Et<sub>2</sub>O.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.95 (9H, s), 1.65 (6H, s), 3.15 (3H, s), 4.00 (2H, s), 8.00 (4H, m).

## EXAMPLE 143

5(R)-3-(1-cyclopropyl-ethoxy)-5-ethyl-5-methyl-4-(4-(methyl sulfonyl)phenyl)-5H-furan-2-one

Step 1: (1-cyclopropylethoxy)acetic acid 2(R)-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one-2-yl ester

The title compound was prepared as described in Example 134 Step 2 using (1-cyclopropylethoxy)acetic acid and 2(R)-2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one from Example 117, Step 3.

Step 2: 5(R)-3-(1-cyclopropylethoxy)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

The title compound was prepared as described in Example 134 Step 3.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.1–0.4 (4H, m), 0.75 (2H, m), 1.00 (1H, m), 1.40 (3H, dd), 1.70 (3H, s), 2.05 (2H, m), 3.20 (3H, s), 4.50 (1H, m), 8.05 (m, 4H).

## EXAMPLE 144

5(S)-5-Ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

Step 1: (±) 2-Methyl-1-(4-(methylsulfonyl)phenyl)-prop-2-en-1-ol

To a solution of 4-bromothioanisole (51 g) in THF (600 mL) cooled to –72° C. was added dropwise a solution of n-BuLi (120 mL, 2.4 M in hexane) over a period of 30 min. The mixture was stirred at –78° C. for 2 h and then a solution of methacrolein (20.3 g) in THF (50 mL) was added over a period of 5 min. The reaction mixture was warmed to –20° C. over a period of 20 min. and then quenched with saturated NH<sub>4</sub>Cl (200 mL) and H<sub>2</sub>O (200 mL). The product was extracted with 500 mL of 1:1 hexane/EtOAc, and dried over MgSO<sub>4</sub>. The extract was filtered and concentrated to give the title compound as a yellow oil (55 g).

Step 2: (±) 2-Methyl-1-(4-(methylsulfonyl)phenyl)-prop-2-en-1-ol

To a solution of the product from Step 1 (55 g., crude) in MeOH (1 L) cooled to 0° C. was added a solution of Oxone® (190 g in 700 mL H<sub>2</sub>O) over a period of 2 h. The mixture was stirred at 5° C. for an additional 3 h and then filtered. The filtrate was concentrated to remove MeOH and

the remaining aqueous mixture was extracted with 1 L of 2:1 EtOAc/hexane. The extract was dried over MgSO<sub>4</sub> filtered and concentrated. The residue was purified by silica gel chromatography eluted with 3:2 hexane/EtOAc to give the title compound (22 g) as a colorless oil.

Step 3: (S)-2-Methyl-1-(4-(methylsulfonyl)phenyl)-prop-2-en-1-ol

To a solution of dry 4A molecular sieves (20 g), and Ti (O<sub>2</sub>Pr)<sub>4</sub> (24.8 mL) in CH<sub>2</sub>Cl<sub>2</sub> (1 L) cooled to –25° C. was added dropwise (+)-diisopropyltartrate (22.4 mL). After stirring at –25° C. for 30 min., a solution of (±)-2-methyl-1-(4-(methylsulfonyl)phenyl)-prop-2-en-1-ol (21 g) in 500 mL of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise, followed by a solution of t-butyl hydroperoxide (20 mL, 5M in decane). The reaction mixture was stirred at –25° C. for 5 h and then quenched with 500 mL of 10% aqueous solution of tartaric acid. After stirring for 1 h, the CH<sub>2</sub>Cl<sub>2</sub> layer was separated, dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel chromatography eluted first with 3:1 hexane/EtOAc followed by 1:2 hexane/EtOAc to give the title compound as a white solid (9 g).

Step 4: (R)-(2-Methyloxiran-2-yl)-(4-methanesulfonyl)phenyl-methanol

Following the same procedure described in Step 3 using 15 g of 4A molecular sieves, 500 mL of CH<sub>2</sub>Cl<sub>2</sub>, 12.4 mL of Ti(OiPr)<sub>4</sub>, 11.2 mL of (–)-diisopropyl tartrate, 20 mL of SM tBuOOH in decane and 9.8 g of the product from Step 3, the title compound (7.6 g, white solid) was obtained.

Step 5: (R)-[(1-Ethoxy-ethoxy)-(4-methanesulfonyl)phenyl]-methyl-2-methyloxirane

To a solution of the product from Step 4 (7.2 g) and ethylvinyl ether (50 mL) in 200 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to 0° C. was added 50 mg of camphorsulfonic acid. The reaction mixture was stirred at r.t. for 20 min. and then treated with 1 mL of Et<sub>3</sub>N, concentrated to give the crude title compound (9 g).

Step 6: (R,S)-1-(1-Ethoxy-ethoxy)-2-methyl-1-(4-methylsulfonyl)phenyl)-butan-2-ol

To a suspension of CuI (20 g) in EtO (450 mL) cooled at –40° C. was added dropwise a solution of MeLi (150 mL, 1.4 M in Et<sub>2</sub>O). After stirring at –40° C. for 20 min., a solution of the crude product from Step 7 (9 g) in 50 mL of Et<sub>2</sub>O was added. The reaction mixture was stirred at –40° C. for 30 min. and then quenched with 20 mL of MeOH and 300 mL of saturated NH<sub>4</sub>Cl solution. Air was bubbled into the mixture with stirring at r.t. for 1 h. The resulting mixture was then extracted with 400 mL of Et<sub>2</sub>O and the Et<sub>2</sub>O extract was dried over MgSO<sub>4</sub> and concentrated to give the crude title compound (10 g) which was used for next step without further purification.

Step 7: (R,S)-2-Methyl-1-(4-(methylsulfonyl)phenyl)-butane-1,2-diol

A solution of the crude product from Step 8 (10 g) in 200 mL of THF, 50 mL of AcOH and 50 mL of H<sub>2</sub>O was heated at 50° C. for 15 h. The mixture was then concentrated to give the crude title compound (7 g) which was used for next step with further purification.

Step 8: (S)-2-Hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl)-butan-1-one

To a solution of the crude product from Step 7 (7 g) and (Bu<sub>3</sub>Sn)<sub>2</sub>O (30 mL) in 150 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled at 10° C. was added a solution of Br<sub>2</sub> (9.3 g in 30 mL of CH<sub>2</sub>Cl<sub>2</sub>). After stirring at r.t. for 30 min. the mixture was diluted with a solution of KF (500 mL, 3N) and 500 mL of Et<sub>2</sub>O. The solid generated was removed by filtration and the filtrate was separated. The organic layer was dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel chro-

## 131

matography eluted with 1:1 hexane/EtOAc to give 5 g of the title compound as a yellow oil.

$^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  8.31 (2H, d), 8.00 (2H, d), 4.67 (1H, s), 3.18 (3H, s), 2.00 (1H, m), 1.30 (1H, m), 1.50 (3H, s), 0.90 (3H, t).

Step 9: 5(S) 5-ethyl-S-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

The title compound was prepared as described in Example 1 Step 4 using 2-propoxyacetic acid and 2(S) 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  0.75–0.83 (3H, m), 1.24–1.30 (6H, m), 1.67 (3H, s), 2.01–2.08 (2H, m), 3.18 (3H, s), 5.17–5.27 (1H, m), 8.00–8.07 (4H, m).

## EXAMPLE 146 AND 147

3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one (146) and 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one (147)

The racemate of Example 134 was separated on a HPLC CHIRALPAK AD (Daicel) column with 10% isopropanol in hexane.

## EXAMPLE 148

3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

The title compound was prepared as described in Example 141 using 5,5-dimethyl-3-hydroxy-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one and (bromomethyl)cyclopropane.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  0.30 (2H, m), 0.55 (2H, m), 1.15 (1H, m), 1.60 (6H, s), 3.20 (3H, s), 4.20 (2H, d), 8.00 (4H, s).

## EXAMPLE 149

5,5-dimethyl-3-(isobutoxy)-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

The title compound was prepared as described in Example 141 using 5,5-dimethyl-3-hydroxy-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one and 1-bromo-2-methylpropane.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  0.90 (6H, d), 1.65 (6H, d), 1.95 (1H, m), 3.20 (3H, s), 4.10 (2H, d), 8.00 (4H, m).

## EXAMPLE 150

3-(4-Bromophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 1, the title compound was prepared from bromophenoxy acetic acid.

M.P.: 150–152° C.  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.77 (6H, s), 3.15 (3H, s), 7.07 (2H, d), 7.46 (2H, d), 7.92 (2H, d), 8.02 (2H, d).

## EXAMPLE 53

3-(6-Amino-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-6-aminopyridine.

M.P.: 165–166° C.  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.74 (6H, s), 3.14 (3H, s), 5.52 (2H, s, br), 6.17 (1H, d), 6.24 (1H, d), 7.41 (1H, t), 7.90 (2H, d), 8.02 (2H, d).

## EXAMPLE 31

3-(2-Quinolinoxyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxyquinoline. M.P.: 141–142° C.

## 132

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.83 (6H, s), 3.11 (3H, s), 7.26 (1H, m), 7.52 (1H, m), 7.70 (1H, m), 7.77 (1H, m), 7.93–8.02 (5H, m), 8.39 (1H, s).

## EXAMPLE 50

3-(2-Chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 2-chloro-5-hydroxypyridine. M.P.: 196–197° C.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.78 (6H, s), 3.16 (3H, s), 7.33 (1H, m), 7.68 (1H, m), 7.94 (2H, d), 8.04 (2H, d), 8.14 (1H, m).

## EXAMPLE 159

3-(6-benzothiazolyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 6-hydroxybenzothiazole. M.P.: 212° C.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.79 (6H, s), 3.10 (3H, s), 7.34 (1H, s), 7.86 (1H, d), 7.93–8.00 (5H, m), 9.15 (1H, s).

## EXAMPLE 160

3-(6-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 6-chloro-2-hydroxypyridine. M.P.: 119–121° C.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.78 (6H, s), 3.15 (3H, s), 7.10 (1H, d), 7.25 (1H, d), 7.89–8.06 (5H, m).

## EXAMPLE 161

3-(4-Quinazolyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 4-hydroxyquinazoline. M.P.: 174–177° C.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  1.76 (6H, s), 3.12 (3H, s), 7.58 (1H, t), 7.67 (1H, d), 7.76 (2H, d), 7.85 (1H, t), 8.03 (2H, d), 8.16 (1H, d), 8.22 (1H, t).

## EXAMPLE 162

(5R)-3-(5-Fluoro-2-pyridyloxy)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one (prepared similarly to the compound of Example 5, Step 1 but using the 2-(R) compound of Example 117, Step 3) and 5-fluoro-2-hydroxy-pyridine. M.S.: ( $\text{Cl}$ ,  $\text{CH}_4$ )  $m/z$  392 ( $\text{M}+\text{H}$ )<sup>+</sup>

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  0.95 (3H, t), 1.76 (3H, s), 2.12 (2H, m), 3.15 (3H, s), 7.18 (1H, m), 7.73 (1H, m), 7.91 (2H, d), 8.02–8.07 (3H, m).

## EXAMPLE 163

(5R)-3-(4-Fluorophenoxy)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described in Example 1, Step 4, the title compound was prepared using (2R)-2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one (Example 117, Step 3) and 4-fluorophenoxy acetic acid. M.P.: 96.8–97.4° C.

$^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  0.92 (3H, t), 1.77 (3H, s), 2.11 (2H, q), 3.14 (3H, s), 7.08–7.11 (4H, m), 7.9 (2H, d), 8.02 (2H, d).



## 133

## EXAMPLE 164

(5R)-3-(5-Fluoro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl) phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluorobutan-1-one (Example 130, Step 3) and 5-fluoro-2-hydroxypyridine.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.94 (3H, s), 3.15 (3H, s), 3.24 (2H, q), 7.20 (1H, m), 7.75 (1H, m), 7.98–8.07 (5H, m).

## EXAMPLE 165

3-(1-Isoquinolinylxy)-5,5-dimethyl-4-(methylsulfonyl) phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 1-hydroxyisoquinoline. M.P.: 193.5–194.5

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75 (6H, s), 3.12 (3H, s), 6.57 (1H, d), 7.27 (1H, d), 7.50–7.76 (5H, m), 8.02 (2H, d), 8.24 (11H, d).

## EXAMPLE 166

(5R)-3-(4-fluorophenoxy)-5-methyl-4-(4-methylsulfonyl) phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described in Example 1, Step 4, the title compound was prepared using 2-(R)-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-4,4,4-trifluoro-1-butanone (Example 130, Step 2) and 4-fluorophenoxyacetic acid. M.P.: 104.7–107.0° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.94 (3H, s), 3.15 (3H, s), 3.27 (2H, m), 7.07–7.13 (4H, m), 7.98–8.04 (4H, m), M.S.: (Cl, CH<sub>4</sub>) m/z 463 (M+H)<sup>+</sup>

## EXAMPLE 167

3-(3-Fluoro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl) phenyl-5H-furan-2-one

Following the procedure described for Example 5, the title compound was prepared using 3-fluoro-2-hydroxypyridine. M.P.: 156–157° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.78 (6H, s), 3.14 (3H, s), 7.23 (1H, m), 7.72 (1H, m), 7.91 (2H, d), 7.96 (1H, d), 8.03 (2H, d).

## EXAMPLE 168

(5R)-3-(3,4-difluorophenoxy)-5-methyl-4-(4-methylsulfonyl) phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluorobutan-1-one (Example 130, Step 3) and 3,4-difluorophenol.

## EXAMPLE 169

(5R)-3-(5-chloro-2-pyridyloxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl) phenyl-5H-furan-2-one

To a solution of 2-(R)-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-1-butanone (800 mg, 30 mmol), Example 117, Step 3, in 24 mL of acetonitrile was added chloroacetic acid (383 mg), CMC (1.7 g) and DMAP (20 mg). The mixture was then stirred at r.t. for 4 hours. Then 5-chloro-2-hydroxypyridine (602 mg) and DBU (1.85 mL) were added and the mixture was stirred for 18 hours. Water was then added to the mixture which was extracted with CH<sub>2</sub>Cl<sub>2</sub>, then washed with 1N HCl, brine, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under vacuum purification by flash chromatography on silica gel 40% EtOAc/Hexane afforded the title compound. M.P.: 191° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.95 (3H, t), 1.76 (3H, s), 2.11 (2H, m), 3.15 (3H, s), 7.18 (1H, d), 7.89–7.93 (3H, m), 8.03 (2H, d), 8.16 (1H, d).

## 134

## EXAMPLE 170

3-(3,4-difluorophenoxy)-5-methyl-5-trifluoromethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-Trifluoromethyl-2-trimethylsilyloxypropionitrile

A mixture of 1,1,1-trifluoroacetone (8.9 mL, 0.1 mmol), trimethylsilylcyanide (13.3 mL, 0.1 mmol) and zinc iodide (5 mg) was stirred for 18 hours, to afford the title compound. Step 2: 2-Hydroxy-1-(4-methylthio)phenyl-2-trifluoromethyl propanone

To a solution of 4-bromothioanisole (19 g, 94 mmol) in THF (200 mL) at –78° C. was added 1.33 M n-Butyl lithium (71 mL, 94 mmol). The mixture was stirred for 1 hr at –78° C. then 10 g (47 mmol) of the compound from Step 1 was added and the mixture was left to warm to r.t. The reaction mixture was quenched with 25% NH<sub>4</sub>OAc extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated to afford 9.7 g of the title compound. Step 3: 2-Hydroxy-1-(4-methylsulfonyl)phenyl-2-trifluoromethyl propanone

Following the procedure described in Example 117, Step 3, and using the compound from the previous step, the title compound was obtained.

Step 4: 3-(3,4-difluorophenoxy)-5-methyl-5-trifluoromethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described in Example 1, Step 4, and using the compound obtained in the previous step, the title compound was obtained. M.P.: 154.1° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 2.06 (3H, s), 3.15 (3H, s), 6.98 (1H, s), 7.7 (1H, m), 7.26 (1H, dd), 7.77 (2H, d), 8.02 (2H, d).

## EXAMPLE 171

3-(3,4-Difluorophenoxy)-5-methyl-4-(4-methylsulfonyl) phenyl-5-propyl-5H-furano-2-one

Step 1: 2-Methyl-1-(4-methylthiophenyl)-pentan-1-one

Following the procedure described for Example 1, Step 1, the title compound was prepared from 2-methylvaleryl chloride and thioanisole.

Step 2: 2-Hydroxy-2-methyl-1-(4-ethylthiophenyl)-pentan-1-one

Following the procedure described for Example 1, Step 2, the title compound was prepared from the product obtained in Step 1.

Step 3: (3,4-Difluorophenoxy)-acetic acid 1-methyl-1-(4-methylthiobenzoylbutyl)ester

A solution of 3,4-difluorophenoxyacetic acid (0.38 g), the product from Step 2 (0.24 g), CMC (1.0 g), and DMAP (100 mg) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was stirred at r.t. for 15 h. The reaction mixture was then treated with saturated solution of NaHCO<sub>3</sub> (20 mL) and extracted with 1:1 EtOAc/hexane (100 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated to give the crude product which was used for next step without further purification.

Step 4: (3,4-Difluorophenoxy)-acetic acid 1-methyl-1-(4-methylsulfonylbenzoylbutyl) ester

A solution of the crude product from Step 3 in 50 mL of 10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH (v/v) was treated with MMPP (1.0 g). The mixture was stirred at r.t. for 30 min. and then diluted with saturated NaHCO<sub>3</sub> solution (50 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated to give the title compound as a white solid.

Step 5: 3-(3,4-Difluorophenoxy)-5-methyl-4-(4-methylsulfonyl) phenyl-5-propyl-5H-furan-2-one

A solution of the product from Step 4, CF<sub>3</sub>CO<sub>2</sub>iPr (0.5 mL) and DBU (0.2 mL) in CH<sub>3</sub>CN (30 mL) was heated to reflux for 30 min. The mixture was then cooled to r.t. treated with ACOH (1 mL) and concentrated. The residue was dissolved in 2:1 EtOAc/hexane (20 mL) and filtered through



## 135

a pad of silica gel. The filtrate was concentrated and the residue was stirred at 5° C. 5:1 hexane/EtOAc (10 mL) for 15 h. The title compound was isolated by filtration as a white solid (380 mg).

<sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 8.04 (2H, d), 7.93 (2H, d), 7.28 (1H, m), 7.12 (1H, m), 6.92 (1H, m), 3.15 (3H, s), 2.06 (2H, m), 1.79 (3H, s), 1.80–1.96 (2H, m), 0.92 (3H, t).

## EXAMPLE 174

3-Cyclobutyloxy-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Following the procedure described for Example 14, the title compound was obtained using cyclobutyloxyacetic acid. M.P. 111–112° C.; Ms (Cl, CH<sub>4</sub>) m/z 337 (M+H)<sup>+</sup>; anal. calcd. for C<sub>17</sub>H<sub>20</sub>O<sub>5</sub>S: C, 60.70; H, 5.99; S, 9.53; found: C, 60.39; H, 6.05; S, 9.60.

## EXAMPLE 175

3-(1-Indanyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 14, the title compound was obtained using 1-indanyloxyacetic acid. M.p. 128–129° C.; MS (Cl, CH<sub>4</sub>) m/z 398 (M+H)<sup>+</sup>; and anal. calcd. for C<sub>22</sub>H<sub>22</sub>O<sub>5</sub>S: C, 66.31; H, 5.56; S, 8.05; found: C, 66.27; H, 5.47; S, 8.34.

## EXAMPLE 176

3-(2-Indanyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 14, the title compound was obtained using 2-indanyloxyacetic acid. M.p. 142–143° C.; Ms (Cl, CH<sub>4</sub>) m/z 399 (M+H)<sup>+</sup>; anal. calcd. for C<sub>22</sub>H<sub>22</sub>O<sub>5</sub>S: C, 66.31; H, 5.56; found: C, 66.50; H, 5.64.

## EXAMPLE 177

3-Cyclopentyloxy-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Following the procedure described for Example 109 the title compound was prepared from cyclopentyl bromide. M.P.: 121–122° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.55–1.85 (8H, m), 1.65 (6H, s), 3.15 (3H, s), 5.43 (1H, m), 7.98–8.07 (4H, m).

## EXAMPLE 178

3-(3,3-Dimethylcyclopentyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Step 1: 3,3-Dimethylcyclopentanol

To a solution of 4,4-Dimethyl-2-cyclopenten-1-one (1.65 g, 15 mmol) in EtOAc (50 mL) was added palladium on activated carbon (270 mg). The resulting suspension was vigorously stirred under an hydrogen atmosphere for 22 hours. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (150 mL) and filtered on a pad of silica gel washed with EtOAc. The solvents were removed by distillation under atmospheric pressure using a 15 cm Vigreux column. The distillation residue was dissolved in MeOH (50 mL) cooled to 0° C. and sodium borohydride (304 mg, 8 mmol) was added and the reaction mixture was stirred at r.t. for 24 h. The reaction was diluted with NH<sub>4</sub>OAc eq. 25% w/r and extract with EtOAc. The organic layer was separated, dried over MgSO<sub>4</sub> and concentrated. Purification by silica gel chromatography (50% Et<sub>2</sub>O/pentane) provided 1.14 g of the title compound as a colorless liquid.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.94 (3H, s), 1.07 (3H, s), 1.25–1.4 (2H, m), 1.55–1.63 (2H, m), 1.67 (1H, dd), 1.85–1.95 (1H, m), 3.42 (1H, d), 4.27 (1H, m).

Step 2: 3-Iodo-1,1-dimethylcyclopentane

## 136

To a 0° C. solution of 3,3-Dimethylcyclopentanol (Step 1) (1.14 g, 10 mmol) and triethylamine (2.0 mL, 14.3 mmol) in dichloromethane was added dropwise methanesulfonyl chloride (1.0 mL, 12.9 mmol). The reaction was allowed to proceed for 30 min. at 0° C., then it was diluted with water and extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. The resulting residue was dissolved in acetone (50 mL), cooled to 0° C. and lithium iodide (6.68, 50 mmol) was added. The resulting suspension was stirred at r.t. for 20 hours. Most of the solvent was removed in vacuo, the residue was taken in EtOAc and washed twice with water. The organic layer was dried over MgSO<sub>4</sub> and concentrated. This crude product was purified by flash chromatography eluted with 40 Et<sub>2</sub>O/pentane to give the title compound as a colorless oil.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.98 (3H, s), 1.14 (3H, s), 1.38–1.46 (1H, m), 1.57–1.64 (1H, m), 1.93 (1H, dd), 2.06–2.16 (2H, m), 2.29 (1H, m), 4.38 (1H, quintet)

Step 3:

Following the procedure described for Example 109, the title compound was prepared from 3-iodo-1,1-dimethylcyclopentanol (Step 2). M.P.: 99–100° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.93 (3H, s), 0.99 (3H, s), 1.32–1.40 (1H, m), 1.48–1.62 (2H, m), 1.65 (6H, s), 1.74 (1H, dd), 1.78–1.88 (1H, m), 1.93–2.02 (1H, m), 3.17 (3H, s), 5.90 (1H, m), 8.02 (4H, dm).

## EXAMPLE 179

3-Isopropoxy-5-methyl-4-(4-methylsulfonylphenyl)-5-propyl-5H-furan-2-one

Following the procedure described for Example 171, the title compound was prepared from isopropoxyphenyl acetic acid. M.P.: 95–96° C.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.88 (3H, t), 1.12–1.32 (2H, m), 1.28 (6H, 2d), 1.67 (3H, s), 2.00 (2H, m), 3.17 (3H, s), 5.22 (1H, heptet), 8.04 (4H, s).

## EXAMPLE 180

3-(2-Methoxy-5-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Step 1: 5-Hydroxy-2-methoxypyridine

To 6M aqueous HCl (20 mL) at 00 C was added 5-amino-2-methoxypyridine (3.1 g, 25mmol), stirred for 10 min and a solution of 4M aqueous NaNO<sub>2</sub> (7 mL, 28 mmol) was added dropwise over a period of 10 min. After further stirring for 30 min, 60% HPF<sub>6</sub> (2 mL) was added and precipitate formed immediately. The mixture was stirred for 15 min, H<sub>2</sub>O (50 mL) was added. The precipitate was collected, washed with H<sub>2</sub>O (3x) and dried under vacuum to give the corresponding diazonium salt as brown powders (6.5 g, 92%).

The above diazonium salt in acetic anhydride (25 mL) was heated at 100–1100 C for 1 h. Solvent was evaporated in vacuo. The residue was diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O. Solid residue was filtered and the ethereal layer was separated, washed with saturated aq. NaHCO<sub>3</sub> brine, dried (anhydrous MgSO<sub>4</sub>) and concentrated to provide the 5-acetoxy-2-methoxypyridine as a brown oil (600 mg).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 2.26 (3H, s), 3.85 (3H, s), 6.78 (1H, d), 7.48 (1H, dd), 7.92 (1H, d).

To a solution of the 5-acetoxy-2-methoxypyridine (600 mg, 3.59 mmol) in MeOH (10 mL) was added 1M aq. NaOH (10 mL, 10 mmol). After stirring at r.t. for 30 min, volatile solvent was removed in vacuo, acidified with HOAc and extracted with CHCl<sub>3</sub> (3x). The combined CHCl<sub>3</sub> extracts were washed with H<sub>2</sub>O, dried (anhydrous MgSO<sub>4</sub>) and evaporated to give the title compound as a brown oil (240 mg, solidified on standing).

## 137

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 3.78(3H, s), 6.60(1H, d), 7.20(1H, dd), 7.70(1H, d), 8.20(1H, br s).

Step 2: 3-(2-Methoxy-5-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 5-hydroxy-2-methoxypyridine.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75(6H, s), 3.16(3H, s), 3.85(3H, s), 6.66(1H, d), 7.47(1H, dd), 7.90(2H, d), 7.95(1H, d), 8.04(2H, d).

## EXAMPLE 181

3-(5-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-Hydroxy-5-methylpyridine

Following the procedure described for Example 48, step 1, the title compound was prepared from 2-amino-5-picoline.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 2.05(3H, s), 6.36(1H, d), 7.24(1H, d), 7.35(1H, dd).

Step 2: 3-(5-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-5-methylpyridine.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75(6H, s), 2.28, 3.16(3H, s), 6.98(1H, d), 7.68(1H, dd), 7.90(2H, d), 7.96(1H, d), 8.04(2H, d).

## EXAMPLE 184

(5RS)-3-(3,4-Difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Step 1: 2(RS)-2-Methyl-1-(4-(methylthio)phenyl)-4,4,4-trifluoro-1-butanone

Following the procedure described for example 1, step 1, the title compound was prepared from 2(RS)-2-methyl-4,4,4-trifluoro-butyl chloride(GB 2238790-A) and thioanisole.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.22(3H, d), 2.30(1H, m), 2.52(3H, s), 2.82(1H, m), 3.88(1H, m), 7.35(2H, d), 7.92(2H, d). Step 2: 2-(RS)-2-Hydroxy-2-methyl-1-(4-(methylthio)phenyl)-4,4,4-trifluoro-1-butanone

To 2-(RS)-2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)-4,4,4-trifluoro-1-butanone(12 g, 45.8 mmol) and triethyl phosphite(16 mL) in DMF(250 mL) at -10° C. was added 1M t-BuOK(46 mL, 46 mmol) in t-BuOH and air was bubbled through the mixture for 3 h. After quenching with 2.5M aq. HOAc(20 mL), the mixture was diluted with H<sub>2</sub>O, extracted with Et<sub>2</sub>O. The etheral extract was washed with H<sub>2</sub>O (2x), 0.5M aq. NaOH, dried(anhydrous MgSO<sub>4</sub>) and concentrated. Chromatography over silica gel and elution with hexanes:EtOAc(4:1) gave the title compound as a yellow oil(6.0 g, ~90% pure).

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.62(3H, s), 2.54(3H, s), 2.70-3.20(2H, m), 7.32(2H, d), 8.15(2H, d).

Step 3: 2-(RS)-2-Hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-4,4,4-trifluoro-1-butanone

To a solution of 2-(RS)-2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)-4,4,4-trifluoro-1-butanone(6.0 g, 21.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub>(200 mL) was added mCPBA(12 g, Aldrich 27,303-1, 57-86%) at 0° C. The mixture was slowly warmed to r.t. over a period of 1 h, washed with 1M aq. NaOH(2x), brine, dried(anhydrous MgSO<sub>4</sub>) and concentrated. Chromatography over silica gel and elution with hexanes:EtOAc (2:1) provided the title compound(4.0 g, 60%).

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.66(3H, s), 2.70-3.20(2H, m), 3.18(3H, s), 5.35(1H, s), 8.04(2H, d), 8.30(2H, d).

Step 4: (5RS)-3-(3,4-Difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

## 138

Following the procedure described for example 1, step 4, the title compound was prepared from 3,4-difluorophenoxyacetic acid and 2-(RS)-2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-4,4,4-trifluoro-1-butanone. NMR of the title compound is the same as Example 168.

## EXAMPLE 185

3-(3-Chloro-4-methoxyphenoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 3-Chloro-4-methoxyphenoxyacetic acid

To a mixture of hydroquinone(24 g, 0.22 mol) and ethyl bromoacetate(24 mL, 0.22 mol) in DMF(300 mL) was added 10M aq. NaOH(22 mL, 0.22 mol). The mixture was stirred at 0° C. for 1 h, diluted with H<sub>2</sub>O, acidified with 6M aq. HCl and extracted with EtOAc. The EtOAc extract was dried(anhydrous MgSO<sub>4</sub>) and concentrated in vacuo. The residue was swished with Et<sub>2</sub>O to give ethyl 4-hydroxyphenoxyacetate (5.8 g) as a white powder.

Ethyl 4-hydroxyphenoxyacetate(1.5 g, 7.6 mmol) was reacted with SO<sub>2</sub>Cl<sub>2</sub>(1.5 mL) to give ethyl 3-chloro-4-hydroxyphenoxyacetate (700 mg, ~80% pure) as a white powder. To a solution of ethyl 3-chloro-4-hydroxyphenoxyacetate(700 mg, 3.0 mmol) and MeI(0.280 mL, 4.5 mmol) in DMF(5 mL) at 0° C. was added 10M aq. NaOH(0.320 mL, 3.2 mmol). The mixture was stirred at r.t. for 12 h, then diluted with H<sub>2</sub>O and extracted with EtOAc to give ethyl 3-chloro-4-methoxyphenoxyacetate (700 mg).

The above ethyl 3-chloro-4-methoxyphenoxyacetate (700 mg) was hydrolysed with 1M aq. NaOH in THF-MeOH (30 mL, 2:1) to provide the title compound as a white powder.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 3.84(3H, s), 4.70(2H, s), 6.85-7.10(3H, m).

Step 2: 3-(3-Chloro-4-methoxyphenoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for example 1, step 4, the title compound was prepared from 3-chloro-4-methoxyphenoxyacetic acid and 2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenylpropan-1-one (example 1, step 3).

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75(6H, s), 3.14(3H, s), 3.84(3H, s), 6.95-7.20(3H, m), 7.86(2H, d), 8.00(2H, d).

## EXAMPLE 186

(5R)-3-(3-Chloro-4-methoxyphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 1, step 4, the title compound was prepared from 3-chloro-4-methoxyphenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one (Example 117, Step 3).

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 0.94(3H, t), 1.76(3H, s), 2.10(2H, q), 3.15(3H, s), 3.85(3H, s), 6.95-7.20(3H, m), 7.90(2H, d), 8.00(2H, d).

## EXAMPLE 188

(5R)-3-(4-Chlorophenoxy)-5-(2,2,2-trifluoroethyl)-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 1, Step 4, the title compound was prepared from 4-chlorophenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-butan-1-one (Example 130, Step 2).

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.95(3H, s), 3.15(3H, s), 3.25(2H, m), 7.12(2H, d), 7.36(2H, d), 8.02(4H, m).

Analysis calculated for C<sub>20</sub>H<sub>16</sub>ClF<sub>3</sub>O<sub>5</sub>S: C, 52.13; H, 3.50. Found: C, 52.27; H, 3.63.

## 139

## EXAMPLE 189

(5R)-3-(4-Bromophenoxy)-5-(2,2,2-trifluoroethyl)-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 1, Step 4, the title compound was prepared from 4-bromophenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-butan-1-one (Example 130, Step 2).

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.94 (3H, s), 3.15 (3H, s), 3.25 (2H, m), 7.07 (2H, d), 7.50 (2H, d), 8.02 (4H, m).

## EXAMPLE 195

5-Cyclopropylmethyl-3-(3,4-difluorophenoxy)-5-methyl-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-Cyclopropylmethyl-2-methyl-1-(4-thiomethyl)phenyl-propan-1-one

To a cold (-78 ° C.) solution of 1-(4-thiomethyl)phenyl-propan-1-one (900 mg, 5 mmol) in dry THF (15 mL) was added a solution of KHMDS (5.5 mmol, 11 mL). The mixture was warmed to r.t. for 5 min and then cooled to 0° C. Bromomethylcyclopropane (810 mg, 6 mmol) was added. The mixture was warmed to r.t. and stirred for 20 h. Aqueous NH<sub>4</sub>Cl solution was added. The mixture was extracted with EtOAc and the concentrated crude extract was purified by chromatography on silica gel (eluted with 20% EtOAc/hexane) to give 435 mg (37%) of the title compound.

Step 2: 2-Cyclopropylmethyl-2-methyl-1-(4-methylsulfonyl)phenyl-propan-1-one

To a solution of the product of step 1 (435 mg, 1.87 mmol) in a mixture of CH<sub>2</sub>ClCH<sub>2</sub>Cl (10 mL) and methanol (10 mL) was added MMPP (2.3 g 3.7 mmol) in 2 portions. The mixture was stirred at r.t. for 6 h. H<sub>2</sub>O was added and the product was extracted with EtOAc. The extracts were washed with H<sub>2</sub>O and brine, dried and concentrated to an oil. The crude oil was purified by chromatography on silica gel (eluted with 30% EtOAc/hexane) to give 363 mg (83%) of the title compound.

Step 3: -Cyclopropylmethyl-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-propan-1-one

To a mixture of the product of step 2 (310 mg, 1.16 mmol), CCl<sub>4</sub> (268 mg, 1.74 mmol), Aliquat 336® (75 mg, 0.185 mmol) and toluene (293 mg, 3.19 mmol) was added powdered NaOH (102 mg, 2055 mmol) in portions. Aqueous NH<sub>4</sub>Cl solution was added. The mixture was neutralized with 1N HCl and extracted with EtOAc and the concentrated crude extract was purified by chromatography on silica gel (eluted with 30% EtOAc/hexane) to give 124 mg (38%) of the title compound.

Step 4: 5-Cyclopropylmethyl-3-(3,4-difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 117, the title compound was prepared from the product of step 3 and 3,4-difluorophenoxyacetic acid.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ -0.01 (1H, m), 0.19 (1H, m), 0.42 (1H, m), 0.51 (1H, m), 0.71 (1H, m), 1.82 (3H, s), 1.87 (1H, dd), 2.26 (1H, dd), 3.15 (3H, s), 6.95 (1H, m), 7.14 (1H, m), 7.29 (1H, q), 8.05 (4H, q).

## EXAMPLE 196

(5R)-3-(3-Fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 3-fluorophenol and (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one, prepared as in Example 162.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 0.93 (3H, t), 1.79 (3H, s), 2.13 (2H, q), 3.15 (3H, s), 6.89 (3H, m), 7.46 (1H, q), 7.93 (2H, d), 8.05 (2H, d).

## 140

## EXAMPLE 197

(5R)-3-(4-Chloro-3-fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 4-chloro-3-fluorophenoxyacetic acid and (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 0.94 (3H, t), 1.80 (3H, s), 2.13 (2H, q), 3.15 (3H, s), 6.95 (1H, m), 7.10 (1H, m), 7.48 (1H, t), 7.94 (2H, d), 8.04 (2H, d).

## EXAMPLE 198

(5R)-3-(3-Phenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from phenol and (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenylbutan-1-one, prepared as in Example 162.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 0.94 (3H, t), 1.78 (3H, s), 2.15 (2H, q), 3.14 (3H, s), 7.09 (3H, m), 7.33 (2H, m), 7.93 (2H, d), 8.01 (2H, d).

Analysis calculated for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>S: C, 64.50; H, 5.41. Found: C, 63.94; H, 5.48.

## EXAMPLE 199

(5R)-3-(4-Chloro-3-methylphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 4-chloro-3-methylphenol and (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one, prepared as in Example 162.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 0.93 (3H, t), 1.78 (3H, s), 2.12 (2H, q), 2.30 (3H, s), 3.15 (3H, s), 6.91 (1H, dd), 7.04 (1H, d), 7.30 (1H, d), 7.92 (2H, d), 8.02 (2H, d).

Analysis calculated for C<sub>21</sub>H<sub>21</sub>ClO<sub>5</sub>S: C, 59.93; H, 5.03. Found: C, 59.59; H, 5.02.

## EXAMPLE 200

3-(4-Chloro-3-methylphenoxy)-5-5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 108, the title compound was prepared from 4-chloro-3-methylphenoxyacetic acid and 2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenylpropan-1-one.

<sup>1</sup>H NMR(CD<sub>3</sub>COCD<sub>3</sub>) δ 1.76 (6H, s), 2.79 (3H, s), 3.15 (3H, s), 6.92 (1H, dd), 7.06 (1H, d), 7.28 (1H, d), 7.92 (2H, d), 8.02 (2H, d).

Analysis calculated for C<sub>21</sub>H<sub>19</sub>ClO<sub>5</sub>S: C, 59.04; H, 4.71. Found: C, 59.18; H, 4.78.

## EXAMPLE 201

(5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-methyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Step 1: (5R)-4-methyl-4-(2,2,2-trifluoroethyl)-5-(4-methylsulfonyl-phenyl)-3,6-dioxabicyclo[3.1.0]hexan-2-one

To a 0° C. solution of the chloroacetate (1.16 g, 3 mmol) from step 3, Example 130, in acetonitrile (15 mL) was added DBU (0.491 mL, 3.3 mmol) and the mixture was warmed up to 25° C. After 2 hours, the mixture was poured on icy 1N HCl and ethyl acetate; the organic layer was separated and the aqueous further extracted once with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO<sub>4</sub> and the solvents were removed in vacuo to yield the essentially pure title compound (0.930 g).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.60–1.70 (3H, 2s), 2.50–3.05 (2H, m), 3.13 (3H, s), 4.40–4.30 (1H, 2s), 7.95–8.05 (4H, 2d).

Step 2: (5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-methyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

To a 0° C. mixture of the epoxide (0.930 g) from step 1 in dimethylformamide (3 mL) and isopropanol (12 mL) was added the potassium salt of 5-bromo-2-hydroxypyridine, prepared from 5-bromo-2-hydroxypyridine and one equivalent of 8N KOH followed by evaporation to dryness with toluene and high vacuum drying, (0.742 g, 3.5 mmol) and the mixture was warmed up slowly to reflux for 16 hrs. It was then cooled to room temperature and poured on icy dilute ammonium chloride and ethyl acetate; the organic layer was separated and the aqueous further extracted once with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO<sub>4</sub> and the solvents were removed in vacuo to yield after purification on silica gel (10% acetone/toluene) the title compound (0.380 g).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.90(3H,s), 3.15(3H,s), 3.15-3.30(2H,AB), 7.15(1H,d), 7.95-8.10(5H,m), 8.25(1H,d).

#### EXAMPLE 202

(5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-ethyl-5-methyl-5H-furan-2-one

Step 1:

To a 25° C. mixture of (2R)-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one ester (0.896 g, 2.7 mmol) prepared as in Example 162) and 5-bromo-2-hydroxypyridine (0.560 g, 3.2 mmol) in acetonitrile (20 mL) was added DBU (1.5 mL) and the mixture was warmed up to 70-80° C. for 2 hrs. The volatils were then removed in vacuo and the mixture purified on silica gel (10% acetone/toluene) to yield the title compound (0.587 g).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.90-1.0(3H,t), 1.75(3H,s), 2.00-2.15(2H,m), 3.15(3H,s), 7.10-7.15(1H,d), 7.85-8.05(4H,2d), 8.20-8.30(1H,d).

#### EXAMPLE 203

3-(5-Chloro-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Step 1: 3-(5-Nitro-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

A suspension made of the alcohol (2.82 g, 10 mmol) from step 1 Example 109, 3-nitro-6-chloro-2-picoline [C.A.70:114970s] (2.06 g, 12 mmol) and 10N NaOH (1.11 mL) in DMF (35 mL) was warmed up to 105° C. for 8 hrs. It was then cooled to room temperature and poured on icy H<sub>2</sub>O and ethyl acetate. The pH was adjusted to c.a. 8 then the organic layer was separated and the aqueous further extracted once with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO<sub>4</sub> and the solvents were removed in vacuo to yield after purification on silica gel (10% acetone/toluene) the title compound (4.180 g).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75(6H,s), 2.70(3H,s), 3.15(3H,s), 7.15-7.20(1H,d), 7.85-8.05(4H,2d), 8.45-8.55(1H,d).

Step 2: 3-(5-Amino-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

A mixture of the compound from the previous step (3.19 g, 7.6 mmol), ammonium chloride (0.250 g) and iron powder (3 g) in ethanol (50 mL) and H<sub>2</sub>O (20 mL) was warmed up to reflux for 1.5 hrs after what it was filtered quickly, while hot, over celite. To the filtrate was added water (250 mL) and ethyl acetate. The organic layer was separated and the aqueous further extracted once with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO<sub>4</sub> and the solvents were removed in

vacuo to yield after purification by swish in diethyl ether the title compound (3.0 g).

<sup>1</sup>H NMR (CD<sub>3</sub>SOCD<sub>3</sub>) δ 1.75(6H,s), 2.10(3H,s), 3.25(3H,s), 4.75-4.85(2H,bs), 6.65-6.70(1H,d), 7.00-7.05(1H,d), 7.80-8.00(4H,2d).

Step 3: 3-(5-chloro-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Sodium nitrite (0.152 g, 2.2 mmol) in H<sub>2</sub>O (1 mL) was added dropwise to a 0° C. suspension of the compound (0.776 g) from the previous step in 6N HCl (4 mL) and the mixture was stirred at 0° C. for 0.5 hr. It was then transferred dropwise into a CuCl (0.396 g, 4 mmol) solution in 12N HCl (3 mL). The reaction mixture was warmed up to 80° C. for c.a. 10 min. then cooled to 25° C. The mixture was poured on icy H<sub>2</sub>O and the pH adjusted to c.a. 4-5 then ethyl acetate was added. The organic layer was separated and the aqueous further extracted once with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO<sub>4</sub> and the solvents were removed in vacuo to yield after purification by swish in diethyl ether the title compound (0.310 g).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.75(6H,s), 2.40(3H,s), 3.15(3H,s), 6.90-7.00(1H,d), 7.75-7.85(1H,d), 7.85-8.05(4H,2d).

#### EXAMPLE 207

3-(1-Cyclopropylethoxy)-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Step 1: 3-Diazo-2,4-(3H 5H)-furanone

To tetrone acid (5.00 g, 49.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (250 mL) at 0° C. were added Et<sub>3</sub>N (8.3 mL, 59.6 mmol) and tosyl azide (7.37 g, 37.4 mmol). After a period of 2 h at r.t., the reaction mixture was partitioned between NH<sub>4</sub>OAc (25%) and CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure. The resulting mixture was purified by flash chromatography (20% to 35% EtOAc in Hexane) to provide 1.4 g of the title compound as a white solid.

Step 2: 3-(1-cyclopropylethoxy)-4-hydroxy-2(5H)-furanone

To the mixture of 3-diazo-2,4-(3H, 5H)-furanone (300 mg, 2.38 mmol; Example 207, Step 1) and α-methylcyclopropanemethanol (2.0 mL) was added rhodium acetate (30 mg). The mixture was heated at 130° C. for a period of 18 h. The excess of alcohol was evaporated under reduced pressure and the resulting crude mixture was purified by flash chromatography (10% to 20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to provide 50 mg of the title compound.

Step 3: 3-(1-cyclopropylethoxy)-4-(4-methylthio)phenyl)-5H-furan-2-one

To a mixture of 3-(1-cyclopropylethoxy)-4-hydroxy-2(5H)-furanone (50 mg, 0.27 mmol; Example 207, Step 2) and diisopropylethylamine (0.066 mL, 0.38 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at -20° C. was added trifluoromethanesulfonic anhydride (0.060 mL, 0.36 mmol). After a period of 5 min. at -20° C., the reaction mixture was brought to 0° C. then to r.t. The reaction mixture was partitioned between NH<sub>4</sub>OAc (25%) and CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure. The title compound was purified by flash chromatography to provide 30 mg of material.

Step 4: 3-(1-cyclopropylethoxy)-4-(4-methylsulfonylphenyl)-5H-furan-2-one

To a mixture of 3-(1-cyclopropylethoxy)-4-(4-methylthio)phenyl)-5H-furan-2-one (30 mg, 0.10 mmol; Example 207, Step 3) in CH<sub>2</sub>Cl<sub>2</sub> ((1.0 mL) MeOH (3.0 mL) were added an excess of OXONE® (150 mg). After the TLC showed completion, the reaction mixture was extracted with EtOAc. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> filtered

and evaporated under reduced pressure. The title compound was purified by flash chromatography to provide 6 mg of material.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.20–0.60 (4H,m), 1.10 (1H, m), 1.45 (3H,d), 3.20 (3H,s), 4.50 (1H,m), 5.30 (2H, s), 8.10 (4H, m).

#### EXAMPLE 208

3-(1-Cyclopropylmethoxy)-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one

The title compound was prepared as described in Example 207.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.40–0.65 (4H,m), 1.30 (1H, m), 3.20 (3H,s), 4.30 (2H, d), 5.30 (2H, s), 8.05 (4H, m).

#### EXAMPLE 209

(RS) 5-Ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

Step 1: (RS) -1-(4-Methylthiophenyl)-2-methyl-1-butanone

To a suspension of AlCl<sub>3</sub> (35.4 g) in CHCl<sub>3</sub> (500 mL) at -10° C. was added dropwise 2-methylbutyryl chloride (31.3 g) followed by thioanisole (31.2 mL). The mixture was then stirred at r.t. for 20 min. and was then cooled back to 0° C. Water (200 mL) was then added over 30 min. The CHCl<sub>3</sub> layer was separated and dried over MgSO<sub>4</sub>. After filtration and removal of the solvent, the residue was dried under vacuum at 80° C. for 2 h to give 35 g of the title compound.

<sup>1</sup>H NMR (300 MHz, acetone d<sub>6</sub>) δ 0.88 (3H, t), 1.12 (3H, d), 1.38–1.50 (1H, m), 1.70–1.85 (1H, m), 3.47 (1H, m), 7.32–7.40 (2H, m), 7.90–8.00 (2H, m).

Step 2: (RS)-2-Hydroxy-1-(4-methylthiophenyl)-2-methyl-1-butanone

To a mixture of the ketone from Step 1 (10 g, 48 mmol) and Aliquat® 336 (20 mL) in CCl<sub>4</sub> (40 mL) and toluene (80 mL) at r.t. was added NaOH pellets (3.8 g, 96 mmol). While stirring vigorously, the mixture was heated briefly to reflux and was then stirred overnight at r.t. After partitioning between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O, the whole was filtered through celite. The organic layer was dried (MgSO<sub>4</sub>), filtered, and evaporated. The residue was purified by flash chromatography (1:10 EtOAc:hexane) to give the title compound as a syrup (5.5 g).

<sup>1</sup>H NMR 6 0.78–0.87 (3H, m), 1.46 (3H, s), 1.74–1.87 (1H, m), 1.92–2.05 (1H, m), 2.54 (3H, s), 4.57 (1H, s), 7.28–7.34 (2H, m), 8.09–8.16 (2H, m).

Step 3: (RS)-2-Hydroxy-1-(4-methanesulfonylphenyl)-2-methyl-1-butanone

To a solution of the tertiary alcohol from Step 2 (4.5 g, 20.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), MeOH (100 mL) and H<sub>2</sub>O (25 mL) was added Oxone® (9 g). After 3 h at r.t. a second 9 g portion of Oxone® was added and the mixture was stirred overnight at r.t. The solvent was then removed under vacuum, and the residue was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was washed with H<sub>2</sub>O and brine, and was then dried (MgSO<sub>4</sub>), filtered, and evaporated. Purification was effected by flash chromatography (1:2 EtOAc: hexane) to give 5.5 g of the title compound as a tan coloured oil.

<sup>1</sup>H NMR (300 MHz, acetone d<sub>6</sub>) δ 0.84–0.92 (3H, m), 1.48 (3H, s), 1.74–1.87 (1H, m), 1.92–2.05 (1H, m), 3.18 (3H,s), 4.73 (1H, s), 7.99–8.05 (2H, m), 8.28–8.34 (2H, m). Step 4: (RS)-1-(4-Methanesulfonylbenzoyl)-1-methylpropyl-2-isopropoxyacetate

To a solution of the tertiary alcohol methyl sulfone from step 3 (2.9 g, 11.3 mmol) and isopropoxy acetic acid (4.0 g, 34 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) is added 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-p-toluenesulfonate (CMC) (10 g, 24 mmol), followed by DMAP (0.66 g, 5.5

mmol). After stirring for 1 h., a further 2.5 g of CMC is added and the reaction is left stirring for an additional 1 h. Water is then added and the product is extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer is dried (MgSO<sub>4</sub>), filtered, and evaporated. Purification is effected by flash chromatography, eluting with 1:6 EtOAc:toluene to give the title compound. Step 5: (RS) 5-Ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

The keto ester from Step 4 is dissolved in CH<sub>3</sub>CN (80 mL) and isopropyl trifluoroacetate (1.2 mL, 8.7 mmol) is added, followed by DBU (1.6 mL, 11 mmol). The resulting solution is stirred for 20 h under gentle reflux. The solvent is then removed under vacuum, and the residue is partitioned between EtOAc and H<sub>2</sub>O. The organic layer is washed with H<sub>2</sub>O and brine, and is then dried (MgSO<sub>4</sub>), filtered, and evaporated. Purification is effected by flash chromatography, eluting with 1:10 EtOAc: toluene to give the title compound.

#### EXAMPLE 210

3-(Cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-(Cyclopropylmethoxy)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester

A 50 L flask was charged with 12 L dry THF and 95% sodium hydride (441 g, 17.5 mol). The internal temperature was reduced to 12° C., and an addition funnel was charged with cyclopropanemethanol (1198 g, 16.6 mol) in 2 L THF. This solution was added to the sodium hydride over 75 min, maintaining an internal temperature below 15° C. The mixture was then warmed to room temperature and stirred 18 h. Sodium chloroacetate (1413 g, 12.1 mol) was added, and the mixture was heated to reflux for 8.5 h, then allowed to cool overnight. The thick slurry was cautiously quenched with water (100 mL), then 10 L of 2M HCl and 8 L of EtOAc were added. The layers were separated and the organic phase was washed with 1.5 L EtOAc. The combined organic phases were concentrated, then partitioned between 12 L EtOAc and 4 L brine. The organic phase was dried over MgSO<sub>4</sub> filtered and evaporated to give 1778 g of a light yellow oil. To this material was added 2-bromo-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (Ex. 109b Step A3, 2742 g, 8.98 mol) and 15 L of anhydrous-EtOH. Ethyldiisopropylamine (1706 g, 13.2 mol) was added and the slurry was heated to reflux, giving a light yellow solution. After 30 h, the solution was allowed to cool with periodic seeding with authentic product. Crystallization began at 46° C. When the internal temperature reached 35° C., 2 L of water was added slowly via an addition funnel. The mixture was cooled to 4° C. in an ice-bath. The suspension was filtered and the crystals were washed with 20% aqueous EtOH (4 L), water (3×4 L), 25% aqueous EtOH (4 L), and ether (3×4 L), then air dried to give the title compound (1843 g, 5.20 mol, 58%).

Step 2: 3-(Cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

A 50 L flask was charged with the ester from Step 2 (1843 g, 5.20 mol), acetonitrile (23 L), isopropyltrifluoroacetate (1300 g, 8.33 mol), and DBU (1067 g, 7.01 mol). The solution was heated to reflux for 18h. The condenser was replaced with a still head, and 10.5 L of solvent was removed over 3 h. The remaining solution was allowed to cool to 30° C., then transferred into 40 L of 0.3 M HCl with vigorous stirring, and seed crystals. The resulting slurry was stirred at room temperature for 18 h, then filtered. The filter cake was washed with 2×5 L water, 2 L of 50% aqueous ethanol, and 3 L of ether. The solid was air-dried for 1 h, then dried under vacuum overnight to give 1859 g of a white solid (still contains residual water). This material was suspended in 8 L

ether, stirred for 26 h, filtered and dried under vacuum to give 1371 g of the title compound. A further 130 g of material was obtained by reprocessing the aqueous acetonitrile and ether filtrate for a total of 1501 g.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.28 (2H, m), 0.53 (2H, m), 1.17 (1H, m), 1.66 (6H, s), 3.17 (3H, s), 4.16 (2H, d), 8.03 (4H, s).

What is claimed is:

1. A compound having the name 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one, or a pharmaceutically acceptable salt or hydrate thereof.

2. A pharmaceutical composition comprising a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

3. A method of treating inflammation in a mammalian patient in need of such treatment comprising administering to said patient a compound according to claim 1 in an amount effective for treating inflammation.

4. A method of treating a mammalian patient for a cyclooxygenase mediated disease comprising administering to a patient in need of such treatment a compound according to claim 1 in an amount which is effective for treating said cyclooxygenase mediated disease.

5. A method in accordance with claim 4 wherein the cyclooxygenase mediated disease is osteoarthritis, or rheumatoid arthritis.

6. A method of treating pain in a mammalian patient in need of such treatment comprising administering to the

patient a compound according to claim 1 in an analgesic effective amount.

7. A compound having the name 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one, or a pharmaceutically acceptable salt or hydrate thereof.

8. A pharmaceutical composition comprising a compound according to claim 7 in combination with a pharmaceutically acceptable carrier.

9. A method of treating inflammation in a mammalian patient in need of such treatment comprising administering to said patient a compound according to claim 7 in an amount effective for treating inflammation.

10. A method of treating a mammalian patient for a cyclooxygenase mediated disease comprising administering to a patient in need of such treatment a compound according to claim 7 in an amount which is effective for treating said cyclooxygenase mediated disease.

11. A method in accordance with claim 10 wherein the cyclooxygenase mediated disease is osteoarthritis, or rheumatoid arthritis.

12. A method of treating pain in a mammalian patient in need of such treatment comprising administering to the patient a compound according to claim 7 in an analgesic effective amount.

\* \* \* \* \*

**“Attachment C”  
Maintenance Fee Statement for  
US Patent No. 5,981,576**



**UNITED STATES DEPARTMENT OF COMMERCE**  
**Patent and Trademark Office**

Address COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D. C. 20231

Customer Num: 909

PILLSBURY WINTHROP, LLP  
P.O. BOX 10500  
MCLEAN VA 22102

## **MAINTENANCE FEE STATEMENT**

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "STAT", below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE CODE	FEE AMT	SUR CHARGE	APPLICATION NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT	ATTY DKT NUM
5,981,576	1551	\$890.00	\$0.00	09/097,537	11/09/99	06/15/98	04	NO	PAID	19548YDA

**DIRECT YOUR RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:**  
**Mail Stop: M. Correspondence, Director of the United States Patent and Trademark Office**  
**P.O. Box 1450**  
**Alexandria, VA 22313-1450**



**“Attachment D”  
Chronology of Major Communication  
with the FDA**

**INAD 010-348, PREVICOX™ (firocoxib) CHEWABLE TABLETS for DOGS  
CORRESPONDENCE SUMMARY 1998-2004**

<b>CORRESPONDENCE DATE</b>	<b>CORRESPONDENCE DESCRIPTION</b>
05/29/1998	Merial request for establishing INAD file for ML-1,785,713 for dogs
06/29/1998	FDA CVM assigns INAD 010-348 to Merial file
08/19/1998	Merial petitions for Expedited Review Status
11/13/1998	Sponsor's Meeting Request and Agenda for developmental plan meeting with CVM
12/04/1998	CVM denial for Expedited Review Status
12/10/1998	Merial - CVM Meeting re developmental plan
01/11/1999	Merial Minutes of 12/10/1998 Meeting
03/08/1999	CVM agreement with Minutes
03/08/2000	Submission of stability testing protocol
05/11/2000	CVM comments on stability protocol
05/31/2000	Submission of four clinical effectiveness protocols for surgical indications
05/31/2000	Submission of target animal safety protocols
05/31/2000	Submission of two clinical effectiveness protocols for musculoskeletal pain
09/28/2000	CVM comments on protocols for musculoskeletal pain
10/06/2000	CVM comments on protocol for soft tissue surgery
10/10/2000	CVM comments on protocol for orthopedic surgery
11/01/2000	CVM comments on target animal safety protocols
12/15/2000	CVM comments on 2 <sup>nd</sup> protocol for soft tissue surgery
12/21/2000	CVM comments on 2 <sup>nd</sup> protocol for orthopedic surgery
01/12/2001	Submission of revised protocols for target animal safety
05/11/2001	Submission of revised protocols for field effectiveness, with revised indication of osteoarthritis
06/12/2001	Submission of revised 10X target animal safety protocol
06/12/2001	Submission of revised 1-3-5X target animal safety protocol
08/13/2001	CVM comments to field effectiveness protocol
08/13/2001	CVM comments to field effectiveness protocol
08/14/2001	Submission of Meeting Request, Agenda and background materials for development plan
08/30/2001	Fax transmission to CVM of draft responses regarding protocols for field effectiveness studies
09/05/2001	Meeting between Merial and CVM to discuss development plan
09/06/2001	Submission of Meeting Request and Agenda for 09/18/01 teleconference regarding study design for protocols PR&D 00535 and PR&D 00538
10/23/2001	Sponsor's Meeting Minutes for 09/05/2001 Meeting
10/23/2001	Submission of final protocols for pivotal US field trials
10/23/2001	Submission of protocol for second pivotal 1-3-5X Target Animal Safety study
10/29/2001	CVM Meeting Minutes for 09/05/01 Meeting
10/31/2001	CVM Meeting Minutes for 09/18/01 teleconference

**INAD 010-348, PREVICOX™ (firocoxib) CHEWABLE TABLETS for DOGS  
CORRESPONDENCE SUMMARY 1998-2004**

<b>CORRESPONDENCE DATE</b>	<b>CORRESPONDENCE DESCRIPTION</b>
08/29/2002	Submission of Dose Rationale, dose titration and confirmation final study reports
09/17/2002	Submission of User/Handler Safety Summary and final study reports for 11 toxicology studies
09/17/2002	Submission of CMC Technical Section
10/10/2002	Submission of pivotal Target Animal Safety Technical Section
10/23/2002	Submission of pivotal Effectiveness Technical Section
10/31/2002	Submission of ex-US, nonpivotal Effectiveness final study reports
11/14/2002	Submission of PKDM final study reports
11/20/2002	CVM concurrence with dose selection
12/23/2002	CVM Incomplete Letter for CMC Technical Section
01/23/2003	CVM response to User/Handler Safety
02/11/2003	Submission of updated User Risk Assessment
02/11/2003	Submission of response to CMC Incomplete
04/02/2003	Submission of updated stability data to CMC
04/10/2003	Submission of draft text labeling
04/14/2003	Submission of miscellaneous pharmacology studies
05/01/2003	Technical Section Complete Letter for CMC
05/21/2003	CVM response to PKDM studies
07/30/2003	Technical Section Complete Letter for Target Animal Safety
07/30/2003	Submission of Request for Categorical Exclusion from preparation of an environmental assessment under the INAD
08/07/2003	Submission of Request for Categorical Exclusion from preparation of an environmental assessment under the NADA
08/15/2003	Technical Section Complete Letter for Effectiveness
09/02/2003	Categorical Exclusion under INAD
09/02/2003	Categorical Exclusion under NADA
09/17/2003	CVM fax transmission of draft FOI Summary
09/23/2003	Technical Section Incomplete Letter for Labeling
09/23/2003	Technical Section Incomplete Letter for FOI Summary
11/05/2003	Submission of response to FOI Summary Incomplete Letter
11/05/2003	Submission of response to Labeling Incomplete Letter
11/26/2003	Submission of All Other Information Technical Section
01/22/2004	Submission of draft labeling by email
02/04/2004	CVM fax transmission of draft labeling
02/11/2004	CVM fax transmission of draft FOI Summary
02/24/2004	Fax transmission to CVM of revised draft label
02/26/2004	CVM draft FOI Summary by email attachment
02/26/2004	Teleconference to resolve label language and FOI
03/03/2004	Fax transmission to CVM of revised draft label and FOI Summary
03/10/2004	Teleconference to resolve label language and FOI
03/15/2004	CVM fax transmission of final label and FOI Summary

**INAD 010-348, PREVICOX™ (firocoxib) CHEWABLE TABLETS for DOGS  
CORRESPONDENCE SUMMARY 1998-2004**

<b>CORRESPONDENCE DATE</b>	<b>CORRESPONDENCE DESCRIPTION</b>
03/17/2004	Submission of Labeling Technical Section
03/18/2004	Submission of update to All Other Information
03/24/2004	Submission of amended facsimile Labeling
03/27/2004	CVM Teleconference Minutes
03/29/2004	Technical Section Complete Letter for All Other Information
03/30/2004	Submission of Sponsor's Teleconference Minutes
04/02/2004	Technical Section Complete Letter for FOI Summary
04/09/2004	Technical Section Complete Letter for Labeling
<del>04/15/2004</del>	<del>Submission of Administrative NADA</del>
05/19/2004	Technical Section Incomplete Letter for CMC Section of Administrative NADA
06/04/2004	Reactivation of Administrative NADA
07/09/2004	Amendment to Reactivation of NADA
<del>07/21/2004</del>	<del>Approval of NADA 141-230</del>